

EXHIBIT B

***In Re: National Collegiate Athletic Association
Student-Athlete Concussion Injury Litigation***

**United States District Court
For The Northern District Of Illinois
Eastern Division**

**MDL No. 2492
Master Docket No. 1:13-cv-09116**

**Expert Report
May 20, 2016**

**Prepared by
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I. Introduction and Summary of Opinions

I have been retained by the National Collegiate Athletic Association¹ in connection with the proposed Second Amended Class Action Settlement Agreement and Release² in the *National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*.³ The Proposed Class Settlement seeks to establish a “Medical Monitoring Program to benefit all persons who played an NCAA-sanctioned sport at an NCAA member institution through the date of preliminary approval, as well as changes to the NCAA’s return-to-play and concussion management policies and guidelines.”⁴

This report supplements my Expert Report in this case dated April 15, 2015 (“First Expert Report”). In my First Expert Report, I analyzed the financial adequacy of the funding for the Medical Monitoring Program. For purposes of this report (“Second Expert Report”), I was asked to analyze participating NCAA member institutions⁵ and NCAA championship sports programs⁶ data to estimate, with a reasonable degree of certainty, the number of unresolved concussions at the School level for five different time periods, described below.

I reviewed information that the NCAA and its counsel provided to me, including NCAA student-athlete data by School and by Sport from 2001 to 2015, concussion data tracked by NCAA’s Injury Surveillance System, documents described in the Data and Documents Considered in Attachment 1, as well as documents described in my First Expert Report.

In its Memorandum Opinion and Order dated January 26, 2016, the Court preliminarily approved the Amended Class Action Settlement Agreement, subject to several proposed modifications. Those modifications included limiting the scope of the class waiver for bodily injury claims “to those instances where the plaintiffs or claimants seek a nationwide class or where the proposed class is comprised of student-athletes from more than one NCAA-affiliated school.”⁷ The Parties have since agreed to modify the class waiver of bodily injury claims so that personal injury or bodily injury claims may be pursued on behalf of a class of persons who allege injury resulting from participation in a single NCAA-sanctioned sport at a single NCAA member school.⁸ Settlement Class Members would release the right to bring single-School / multi-Sport bodily injury claims on a class basis.⁹

¹ Herein referred to as “NCAA”.

² Herein referred to as “Proposed Class Settlement”.

³ Herein referred to as “Class Action”.

⁴ Second Amended Class Action Settlement Agreement and Release, Section I.

⁵ Herein referred to as “Schools”.

⁶ Herein referred to as “Sports”.

⁷ Memorandum Opinion and Order, January 26, 2016 p. 45.

⁸ Second Amended Class Action Settlement Agreement and Release, Section II(RR).

⁹ See *id.*

I have been asked to perform analyses that may assist the Court in assessing the modification of the class waiver of bodily injury claims. Specifically, I was asked to estimate the number of unresolved concussions at the School level over different time periods since 2001 in order to assist the Court in determining whether a putative class including student-athletes at individual Schools could meet certain legal standards associated with class size, specifically numerosity.

During the period 2001/02 through 2015/16, 1,141 Schools participated in 40 different Sports. Based on my analysis and the assumptions included herein, to a reasonable degree of certainty, it is my opinion that less than 4% (36) of Schools will have more than 20 unresolved concussions for the maximum time period 2001-2016 and that none (zero) will have more than 40 unresolved concussions for the same maximum time period.¹⁰ I estimate that a typical School will have 11 unresolved concussions.

I also estimated a reasonable upper bound of unresolved concussions at each School, designed to produce a very conservative high-end figure. The upper bound is based on inherent variability in expected concussions across schools and over time. The unresolved concussion upper bound is an extremely unlikely outcome (<1% chance of occurrence) at any given School, and is calculated using standard statistical concepts described below. It is my opinion that every School's conservative upper bound is fewer than 40 unresolved concussions, and the largest School¹¹ has an upper bound of 35 unresolved concussions. A typical School will have a conservative upper bound of no more than 13 unresolved concussions.

At the request of NCAA, I analyzed several other time periods between 2001 and 2016. By definition, all of the unresolved concussion estimates for these time periods will be less than those in the maximum time period 2001-2016. See Table 1 for a Summary of unresolved concussions for the maximum time period 2001-2016.

¹⁰ The figures expressed in my opinions are gross numbers and do not account for the fact that many, if not most, student-athletes with unresolved concussions will not yet have a documented diagnosis. Accounting for this factor would further decrease these figures and could quite conceivably decrease these figures by material amounts.

¹¹ The largest NCAA School represents the School with the most estimated unresolved concussions. There are several Schools with more student-athletes but fewer estimated unresolved concussions. For example, the School with the most student-athletes has 6,008 student-athletes, of which 37% (2,229) participate in contact Sports, whereas the School with the most estimated unresolved concussions has 5,321 student-athletes, of which 44% (2,367) participate in contact Sports, resulting in a higher number of unresolved concussions.

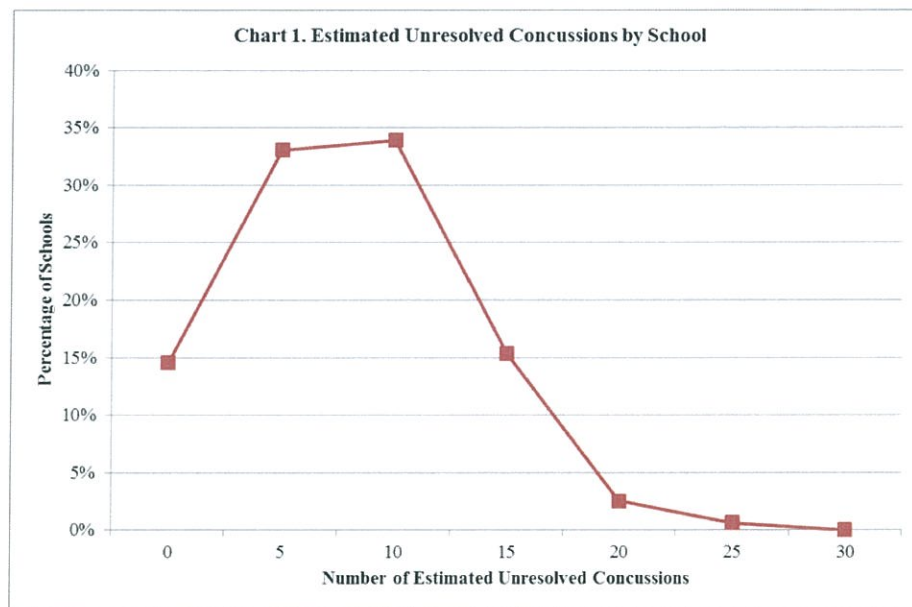
Table 1. Executive Summary Chart

	2001/02 - 2015/16 (Maximum Time Period)			
	Number of Student-Athletes	Estimated Concussed	Estimated Unresolved Concussed	Upper Bound Estimated Unresolved Concussed ^[2]
Largest School ^[1]	5,321	378	29	35
Average School	2,076	140	11	13
Median School	2,017	139	11	13

^[1] The largest School represents the School with the most estimated unresolved concussions.

^[2] Total unresolved concussions will be at or below this level at the 99% confidence level, as described in more detail in the Methodology & Analysis section below.

See Chart 1 below for the distribution of the number of estimated unresolved concussions by School.



My opinions, and the bases for those opinions, are set forth in this Second Expert Report. I reserve the right to supplement this Second Expert Report, if appropriate. Unless otherwise defined, capitalized terms in this Second Expert Report shall have the same meaning as those in the Second Amended Class Action Settlement Agreement and Release.

II. Methodology and Analysis

A. Statistics Regarding Number of Student-Athletes at Each School

In this analysis, I received from the NCAA actual roster size information for every School and Sport from 2001/02 through the 2014/15 season.¹² By analyzing this data I was able to estimate concussions at the School level. At the instruction of counsel, I performed this analysis for multiple time periods between 2001/02 and 2015/16.

Roster sizes vary widely by Sport, and Schools field different numbers of Sports. As such, there is significant variability in the number of student-athletes who participated in Sports at each School. For example, the School with the most student-athletes with unresolved concussions from 2001-2016 offered 28 Sports totaling 5,321 student-athletes.¹³ By contrast, the School with the fewest student-athletes from 2001-2016 offered 1 Sport totaling 19 student-athletes. The median number of Sports by School is 18, and the median number of student-athletes is 2,017.¹⁴

The vast majority of NCAA student-athletes never experience a concussion, even in contact Sports. For purposes of my First Expert Report, I determined that concussion rates range by Sport from 0.0% - 7.38%. While concussion rates vary by Sport, they remain low in the absolute, which limits the total number of concussions experienced at any individual School over any given time period. Among contact Sports, Men's Wrestling has the highest rate, with an average of 7.38 concussions per 100 participants per season. Football, the largest Sport by count, has a lower concussion rate, 3.62%. Concussion rates for other contact Sports range between 1.69% and 6.71%. Non-contact Sports have concussion rates between 0.0% and 2.88%.

B. Statistics Regarding Coaches at Each School

At the NCAA's request, I analyzed head coaches data to determine the extent to which NCAA coaches coach more than one Sport. The coaches data I reviewed provides a comprehensive snapshot of head coaches in 2016.¹⁵ This data lists head coaches, not permanent assistants, student assistants, trainers, etc. It does not track coaching changes over time at a given program.

¹² 2015/16 roster size information was not available at the time of this report. I assumed the same roster composition as 2014/15 for this period.

¹³ There are Schools with more student-athletes, but due to the mix of Sports, I estimate those Schools will have fewer unresolved concussions.

¹⁴ The School offering the largest number of Sports from 2001-16 offered 36 Sports.

¹⁵ NCAA, *All Head Coaches 3.28.16*.

Based on my analysis of the coaches data, Schools employ 14,361 head coaches as of March 2016. 6,230 of those coaches coach contact Sports, while 8,131 coach exclusively non-contact Sports. Furthermore, the data shows the following:

- More than 80% of the coaches (11,619) coach only one Sport.
- More than 18% of the coaches (2,585) coach more than one Sport, all of which are non-contact Sports. Almost half of those individuals who coach more than one Sport coach combinations of track and field and cross-country programs, across men's and women's programs.
- Less than 1% of the coaches (100) coach one contact Sport and one or more non-contact Sport.
 - Only one head football coach also coaches another Sport. This head football coach also coaches Men's golf.
- Less than 0.5% of the coaches (57) coach two contact Sports, all of which are some combination of field hockey, lacrosse, and soccer, across men's and women's programs.
 - No (zero) coaches coach more than two contact Sports.

In summary, the vast majority of coaches coach a single Sport, and it is very rare for coaches to coach multiple contact Sports.

C. Unresolved Concussion Estimates by School

Overall Approach & Data Gathering

In order to estimate unresolved concussions at the School and Sport level, I used a similar set of procedures described in my First Expert Report:

- First, I determined the number of living student-athletes (for a given time period and School) from annual roster data by Sport. I relied upon observed roster sizes for all Sports at all Schools for the 2001/02 through 2014/15 athletic seasons, as tracked by the NCAA.
- Second, I estimated the number of concussed student-athletes within each time period based on Sport-level concussion incidence data tracked by the NCAA Injury Surveillance System from 2009-2012. These concussion rates are based on reported concussions and were adjusted for student-athletes with more than one concussion. The average concussion rates used for the purposes of this analysis are the same as the concussion rates used in my First Expert Report.

- Third, I estimated the number of unresolved concussions based on a 7.5% unresolved concussion rate, which was the most conservative rate in my First Expert Report.

In addition to the steps described above and in my First Expert Report, I performed a variance analysis of the expected number of unresolved concussions by School. This step recognizes that not every School will experience an “average” number of concussions in any given year. Performing a variance analysis enabled me to estimate an upper bound for unresolved concussions at individual Schools. It is important to note, however, that many Schools will have *fewer* concussions than the average, causing overall unresolved concussion levels to revert to the mean in the aggregate. I relied on concussion incidence data tracked by the NCAA’s Injury Surveillance System in order to measure concussion rate variability by School, described in detail below.¹⁶

Lastly, I considered the likelihood that student-athletes would have (1) a documented concussion and (2) a documented diagnosis of a concussion-related disease.

The NCAA requested I perform my analysis for the following date ranges:

Sensitivity 1:	2001/02 - 2015/16	Maximum date range
Sensitivity 2:	2001/02 - 2009/10	Earliest Date to August 2010 Concussion Management Plan (“CMP”) legislation ¹⁷
Sensitivity 3:	2010/11 - 2015/16	August 2010 CMP legislation to present
Sensitivity 4:	2001/02 - 2004/05	Earliest Date to NCAA revised concussion guidelines ¹⁸
Sensitivity 5:	2004/05 – 2009/10	NCAA revised concussion guidelines to CMP legislation

Determine Student-Athlete Size and Estimated Number of Concussions by School

The first step in my analysis is to determine the number of living student-athletes by School and by Sport for each of the five time periods (“Sensitivities”). Because roster count data is not tracked by individual athlete over time, I performed further calculations to estimate the total number of unique student-athletes. Adjustments were made to account for 1) student-athlete participation in more than one season, and 2) the change in roster size of a given Sport at a given School over time.

¹⁶ NCAA, *Confidential NCAA 20160328*. This document anonymizes Schools, thus there is no School or student-athlete-identifying information.

¹⁷ In August 2010, the legislative bodies for all three NCAA divisions adopted legislation requiring member Schools to have concussion management plans.

¹⁸ In 2004, NCAA revised the concussion guidelines in its Sports Medicine Handbook (SMH).

The resulting unique student-athlete counts were adjusted for mortality¹⁹ to arrive at the total number of surviving student-athletes in each Sport at each School for the five Sensitivities analyzed. Consistent with my First Expert Report, I relied upon incidence data tracked by the NCAA Injury Surveillance System from 2009-2012²⁰ to estimate concussion rates by Sport. I then applied these rates to the total surviving student-athlete population to arrive at estimated concussed student-athletes by School.

Next, I estimated the number of unresolved concussions based on the most conservative rate I utilized in my First Expert Report (i.e., 7.5%). Tables 2, 3, 4, and 5 summarize the results by School, demonstrating how few unresolved concussions I estimate at each School.

Table 2. Summary Results - Average School^[1]

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Number of Student-Athletes	2,076	1,332	1,072	714	998
Estimated Concussed	140	91	72	49	68
Estimated Unresolved Concussed	11	7	6	4	6

^[1] Represents the total number of student-athletes, total estimated concussed student-athletes, and total estimated unresolved concussed student-athletes divided by the total number of Schools.

Table 3. Summary Results - Median School^[1]

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Number of Student-Athletes	2,017	1,266	1,042	674	957
Estimated Concussed	139	90	71	48	66
Estimated Unresolved Concussed	11	7	6	4	5

^[1] Represents the midpoint for the total number of student-athletes, the midpoint for the total estimated concussed student-athletes, and the midpoint for the total estimated unresolved concussed student-athletes.

Table 4. Summary Results - Largest School^[1]

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Number of Student-Athletes	5,321	3,557	2,668	2,063	2,916
Estimated Concussed	378	253	190	151	193
Estimated Unresolved Concussed	29	19	15	12	15

^[1] The largest School represents the School with the most estimated unresolved concussions.

¹⁹ "Period Life Table, 2009" *Actuarial Life Table*, Social Security Administration. Web. 21 Jan. 2014.

²⁰ These rates are based on reported concussions. I did not adjust for concussion underreporting as I was instructed by counsel that any such class would require a documented concussion. Rates were adjusted for student-athletes with more than one concussion.

Table 5. Unresolved Concussion Estimates

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Percentage of Schools with 20+ Estimated Unresolved Concussions	3.16%	0%	0%	0%	0%
Percentage of Schools with 40+ Estimated Unresolved Concussions	0%	0%	0%	0%	0%
Largest Estimated Unresolved Concussions	29	19	15	12	15
Average Estimated Unresolved Concussions	11	7	6	4	6
Median Estimated Unresolved Concussions	11	7	6	4	5

Assessed Likelihood of Student-Athletes Having Documented Concussion & Documented Diagnosis

I then considered the likelihood that student-athletes would have a documented concussion and a documented diagnosis of a concussion-related disease. It is my understanding, based on instruction from counsel, that a student-athlete would need to meet both of these requirements to be a member of any proposed class at the School level. These criteria almost certainly will reduce the number of student-athletes eligible, as discussed below.

We can reasonably expect that less than 100% of concussed student-athletes with unresolved symptoms will proactively seek out a diagnosis that would make them eligible for a proposed class at the School level. First, even in the presence of symptoms, patients often delay or never seek diagnosis or treatment.²¹ Second, the oldest student-athlete considered herein would be 36 years old today,²² an age that predates by decades the average age of onset of many long-term medical conditions some believe may be associated with concussions.²³

Although both of these points strongly suggest a documented diagnosis rate of less than 100%, I have very conservatively assumed that all concussed student-athletes with a documented concussion and unresolved symptoms will also have a documented diagnosis. As a result, unresolved concussions presented herein are much higher than the number of student-athletes with a documented concussion and documented diagnosis. In fact, the number of student-athletes with a documented concussion and documented diagnosis may be dramatically lower.

²¹ See studies listed in the Documented Diagnosis section of Attachment 1.

²² The longest time period analyzed herein ranges from 2001/02 - 2015/16. If we assume a student-athlete is 22 years old during the 2001/02 athletic season, that student-athlete would be 36 years old today. While this represents the typical age for a college senior, it is possible a student-athlete was older than 22 during the 2001/02 athletic season, in which case that student-athlete would be older than 36 years old today.

²³ Declaration of Dr. Julian Bailes, *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, MDL No. 2492. Master Docket No. 1:13-cv-09116 (Docket # 222).

D. Variance Analysis

In my First Expert Report, I estimated 325,533 concussed student-athletes out of roughly 4.2 million living student-athletes. This aggregate estimate was calculated using average concussion rates by Sport derived from the NCAA's Injury Surveillance System from 2009-2012. While I expect that observed concussion rates will vary among schools and between seasons, the use of an average concussion rate is appropriate in that context, because I was estimating concussions at the highest level (all Schools, all athletic seasons). In the aggregate and over time, rates revert to the mean.

On the other hand, for the purposes of this report, I estimated unresolved concussions at individual Schools over shorter durations. In order to estimate variability at the School level,²⁴ I utilized observed concussion incidence data from NCAA's Injury Surveillance System for the 2009-2012 period. Concussion counts in this data set were provided by Sport, by School,²⁵ and by athletic season. I divided concussion counts by total reported athlete exposures²⁶ in order to arrive at a concussion rate per athletic exposure ("AE concussion rate") for each Sport/School/athletic season reported in the data, which controls for program size.

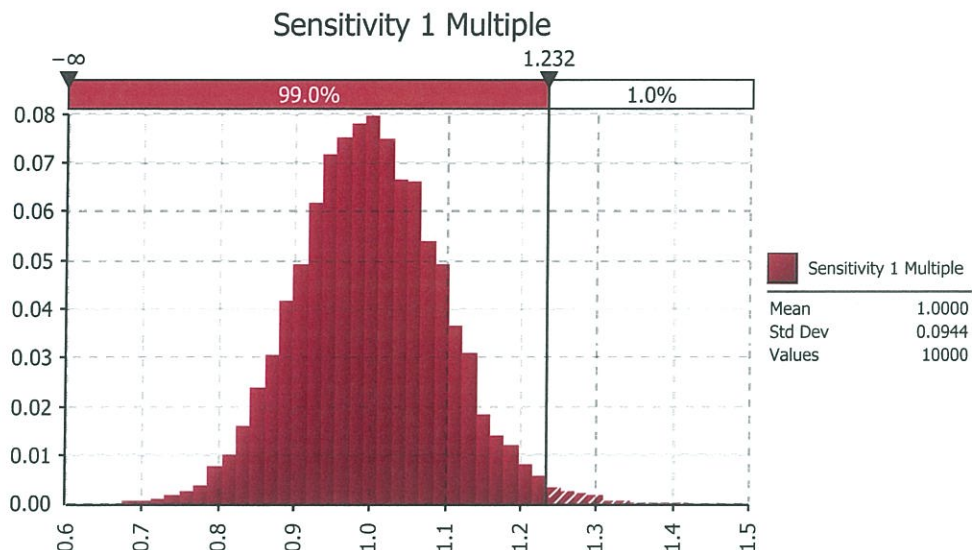
I then performed a statistical analysis using this AE concussion rate data to generate a distribution of potential concussion rates at a given School.²⁷ I expressed the possible concussion rate outcomes as a multiple of the expected, or mean, concussion rate, each of which is assigned a probability. The chart below shows the distribution of multiples for the longest time period. Some outcomes produce concussion rates below the mean (multiple <1), and some outcomes produce concussion rates above the mean (multiple >1). As expected, the mean of all multiples equals 1.

²⁴ This variability analysis captures differences due to inherent randomness between seasons and Schools. It is not intended to identify or measure systemic differences at the School level, to the extent those exist, that may cause concussion rates at a given School to be consistently higher or lower than the average.

²⁵ This data set anonymizes Schools, thus there is no School or student-athlete-identifying information.

²⁶ Defined as one athlete participating in one game or practice in which he/she is exposed to the possibility of athletic injury.

²⁷ Sport-specific concussion rates were weighted by the Sport's estimated share of total concussions at an average School.

Chart 2. Distribution of Multiples, n=15

I determined a reasonable upper bound to be equal to the concussion rate multiple sitting at the 99th percentile of each distribution. As shown above, the multiple at the 99th percentile of the distribution for the longest time period is 1.23. This means I would expect less than 1% of Schools to have observed concussions 23% greater than the number predicted using average concussion rates. The upper bound multiples for all Sensitivities are summarized below. Please refer to Attachment 2 for detailed statistics and additional explanation of the variability analysis.

Table 6. Upper Bound Multiple

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Upper Bound Multiple ^[1]	1.23	1.30	1.36	1.46	1.36

^[1] Multiples tie to the 99th percentile of distributions shown in Charts 2-6 on Attachment 2.

Next, I applied these multiples to the estimated number of concussions by School to arrive at an upper bound for the number of concussions and unresolved concussions by School.

For the longest time period (i.e., 2001-2016), the School expected to have the most unresolved concussions has a 99% likelihood of 35 or fewer unresolved concussions, compared to an expected value of 29 unresolved concussions. The results of this analysis are summarized below.

Table 7. Summary Results - Upper Bound Median School ^[1]

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Number of Student-Athletes	5,234	3,947	2,220	1,373	2,591
Estimated Concussed	171	117	96	70	90
Estimated Unresolved Concussed ^[2]	13	9	8	6	7

^[1] Represents the midpoint for the total number of student-athletes, the midpoint for the total estimated concussed student-athletes, and the midpoint for the total estimated unresolved concussed student-athletes.

^[2] The upper bound of Estimated Unresolved Concussed shown herein is equal to the Estimated Unresolved Concussed shown in Table 3 multiplied by the Upper Bound Multiple shown in Table 6. Some figures may not tie due to rounding.

Table 8. Summary Results - Upper Bound Largest School ^[1]

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Number of Student-Athletes	5,321	3,557	2,668	2,063	2,916
Estimated Concussed	466	329	258	221	261
Estimated Unresolved Concussed ^[2]	35	25	20	17	20

^[1] The largest School represents the School with the most estimated unresolved concussions.

^[2] The upper bound of Estimated Unresolved Concussed shown herein is equal to the Estimated Unresolved Concussed shown in Table 4 multiplied by the Upper Bound Multiple shown in Table 6. Some figures may not tie due to rounding.

During the longest time period, less than 14% of Schools have more than a 1% likelihood of 20+ unresolved concussions, and no (zero) Schools have more than a 1% likelihood of 40+ unresolved concussions. By assigning the upper bound at the 99th percentile, these estimates are very conservative and, by definition, extremely unlikely to occur. The results are summarized below.

Table 9. Upper Bound Unresolved Concussion Estimates

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Percentage of Schools with >1% likelihood of 20+ Estimated Unresolved Concussions	13.76%	1.01%	0%	0%	0%
Percentage of Schools with >1% likelihood of 40+ Estimated Unresolved Concussions	0%	0%	0%	0%	0%
Largest Estimated Unresolved Concussions	35	25	20	17	20

III. Opinions & Conclusions

I performed this analysis to estimate the expected number of unresolved concussions at NCAA Schools (1,141 Schools, each of which offered up to 36 Sports) over different periods. I also performed a variance analysis to determine an upper bound of unresolved concussions at NCAA Schools over each those periods. Based on my analysis and the assumptions included herein, to a reasonable degree of certainty, I formed these opinions and conclusions for the maximum time period (2001 – 2016).

Expected unresolved concussions:

- I expect that no Schools will have over 40 unresolved concussions;
- I expect that less than 4% (36) of Schools will have over 20 and fewer than 40 unresolved concussions (largest School: 29); and
- I expect that a typical NCAA School will have 11 unresolved concussions.

Upper bound number of unresolved concussions:

- I expect no Schools will have over 40 unresolved concussions at the upper bound (largest School: 35); and
- I expect the upper bound for a typical NCAA School will be 13 unresolved concussions.

A handwritten signature in black ink, reading "Ross I. Mishkin", is written over a horizontal line.

Ross I. Mishkin

Attachment 1

Data and Documents Considered

I. Motions, declarations, and other documents related to *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, MDL No. 2492. Master Docket No. 1:13-cv-09116

1. *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, Expert Report of Ross I. Mishkin
4/16/2015
2. *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, Declaration of Dr. Julian E. Bailes
9/14/2015
3. *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, Memorandum Opinion and Order
1/26/2016
4. *In Re: National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation*, Second Amended Class Action Settlement Agreement and Release
5/20/2016

II. Class Member Population and Participation

1. NCAA. *Final_SA_2001_02*. (Microsoft Excel 2003 version) [data file].
2. NCAA. *Final_SA_2002_03*. (Microsoft Excel 2003 version) [data file].
3. NCAA. *Final_SA_2003_04*. (Microsoft Excel 2003 version) [data file].
4. NCAA. *Final_SA_2004_05*. (Microsoft Excel 2003 version) [data file].
5. NCAA. *Final_SA_2005_06*. (Microsoft Excel 2003 version) [data file].
6. NCAA. *Final_SA_2006_07*. (Microsoft Excel 2003 version) [data file].
7. NCAA. *Final_SA_2007_08*. (Microsoft Excel 2003 version) [data file].
8. NCAA. *Final_SA_2008_09*. (Microsoft Excel 2003 version) [data file].
9. NCAA. *Final_SA_2009_10*. (Microsoft Excel 2003 version) [data file].
10. NCAA. *Final_SA_2010_11*. (Microsoft Excel 2003 version) [data file].
11. NCAA. *Final_SA_2011_12*. (Microsoft Excel 2003 version) [data file].
12. NCAA. *Final_SA_2012_13*. (Microsoft Excel 2003 version) [data file].
13. NCAA. *Final_SA_2013_14*. (Microsoft Excel 2003 version) [data file].
14. NCAA. *Final_SA_2014_15*. (Microsoft Excel 2003 version) [data file].
15. NCAA. *Copy of Sport Code List*. (Microsoft Excel 2010 version) [data file codebook].
16. "Period Life Table, 2009" *Actuarial Life Table*, Social Security Administration. Web.
21 Jan. 2014.

III. Coaching

1. NCAA. *All Head Coaches 3.28.2016*. (Microsoft Excel 2010 version) [data file].

IV. Concussions

1. NCAA. *Confidential NCAA 20160328*. (Microsoft Excel 2003 version) [data file].

V. Documented Diagnosis

1. Kannan, Viji Diane. MSPH and P. Veazie, Ph.D. "Predictors of Avoiding Medical Care and Reasons for Avoidance Behavior". *Medical Care*. Apr 2014;52(4):336-45.
2. Persoskie, Alexander, et al. "Association of Cancer Worry and Perceived Risk with Doctor Avoidance: An Analysis of Information Avoidance in a Nationally Representative U.S. Sample". *Journal of Behavioral Medicine*. Oct 2014;37(5):977-87.
3. Taber, Jennifer, Ph.D., Bryan Leyva, B.A., and Alexander Persoskie, Ph.D. "Why do People Avoid Medical Care? A Qualitative Study Using National Data". *Journal of General Internal Medicine*. Mar 2015;30(3):290-7.

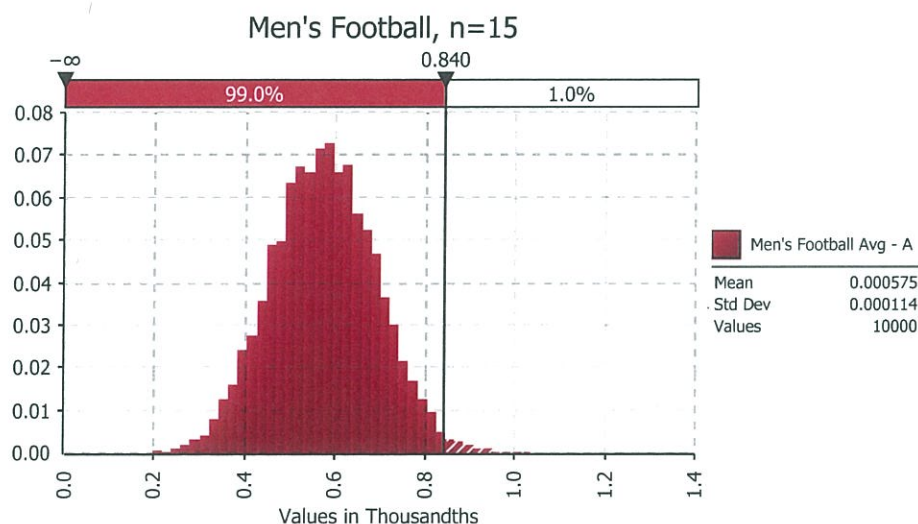
Attachment 2

Variance Analysis – Additional Support

In order to estimate variability at the School level, I utilized observed concussion incidence data from the NCAA's Injury Surveillance System for the 2009-2012 periods. Concussion counts were provided by Sport, by School¹ and by athletic season. To adjust for varying program sizes, I divided concussion counts by total reported athlete exposures in order to arrive at an AE concussion rate for each Sport/School/athletic season reported in the data. These observed AE concussion rates were then used to measure the concussion rate variability in the five Sensitivities analyzed herein.

For the longest time period (i.e., 2001-2016), there are 15 athletic seasons. To analyze variability in Men's Football, for example, I randomly selected 15 observations from the observed AE concussion rates detailed above and calculated the average of these 15 observations. I performed a Monte Carlo simulation, a standard statistical method to perform "what if" scenarios, that repeated this step 10,000 times, producing a distribution of 10,000 averages using a sample size of 15 (n=15). The results of this Monte Carlo simulation for Men's Football are shown in the relative frequency distribution below, showing the 15-year average concussion rate by AE on the x axis and relative frequency on the y axis.²

Chart 1. Distribution of the Sample Means, n=15



As shown in the chart above, 99% of the 10,000 iterations performed in the Monte Carlo simulation (n=15) resulted in an AE concussion rate of less than 0.840. Only 1% of the

¹ This data set anonymizes Schools, thus there is no School or student-athlete-identifying information.

² The areas (height × width) of all the bars add up to 1.

iterations resulted in an AE concussion rate of greater than 0.840, while the mean is 0.575. To measure the potential variance at the School level, it is important to incorporate the expected variance of all Sports. I simultaneously performed a Monte Carlo simulation for all Sports to arrive at a distribution of weighted-average concussion rates at the School level. Each data point in this distribution was then divided by the mean weighted-average concussion rate to derive a distribution of “multiples” (each potential outcome / expected outcome = multiple).

I performed this analysis for all Sensitivities, utilizing a sample size equal to the number of athletic seasons included in each, as summarized below.

Table 1. Athletic Seasons Sample Size

	Sensitivity 1 2001/02 - 2015/16	Sensitivity 2 2001/02 - 2009/10	Sensitivity 3 2010/11 - 2015/16	Sensitivity 4 2001/02 - 2004/05	Sensitivity 5 2004/05 - 2009/10
Athletic Seasons	15	9	6	4	6

I determined a reasonable upper bound to be equal to the multiple sitting at the 99th percentile of each distribution. These distributions are shown below for each Sensitivity. The multiple shown at the 99th percentile of each distribution is also shown on Table 6 of this Second Expert Report.

Chart 2. Distribution of Multiples, n=15

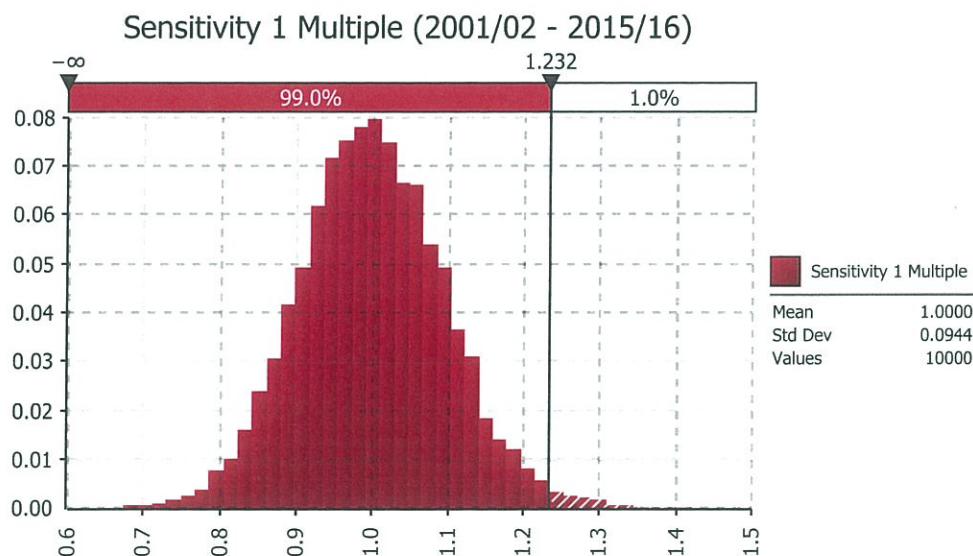


Chart 3. Distribution of Multiples, n=9

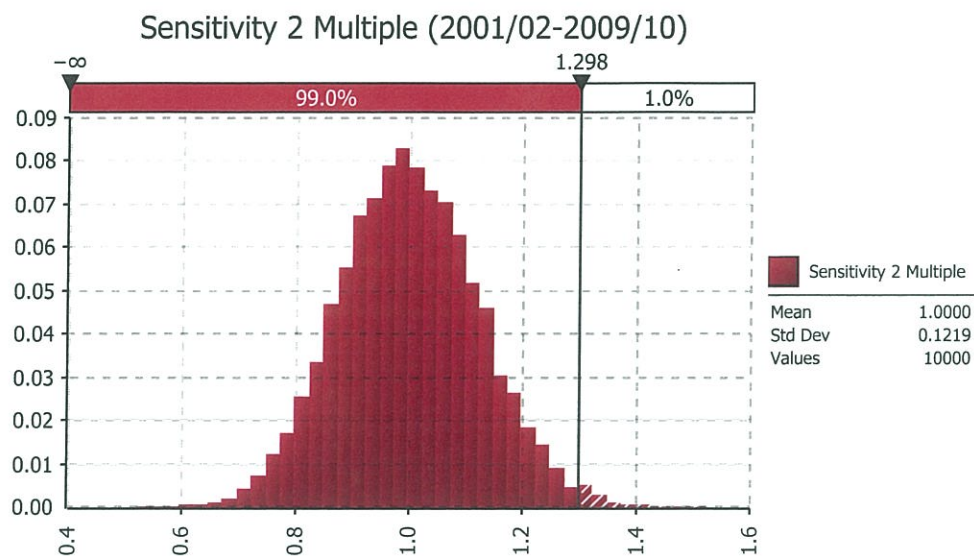


Chart 4. Distribution of Multiples, n=6

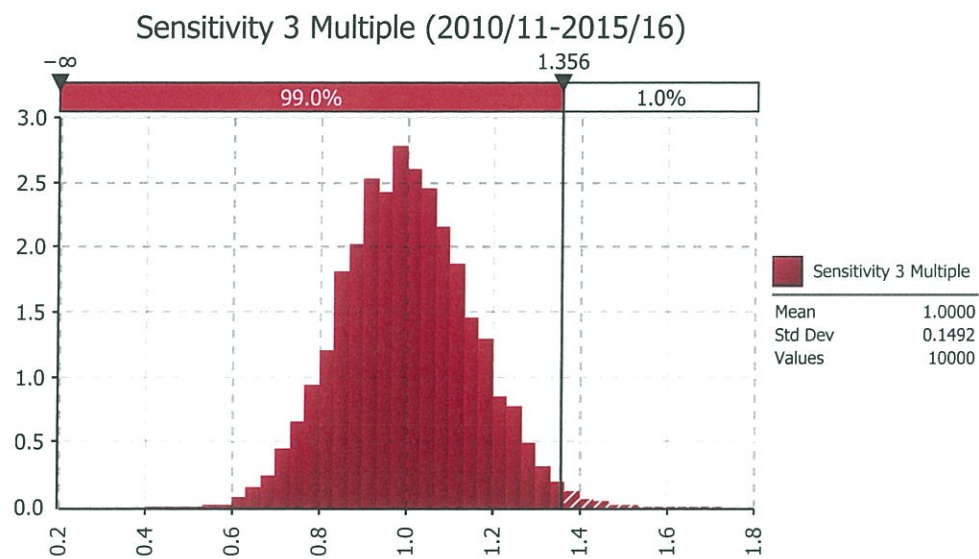


Chart 5. Distribution of Multiples, n=4

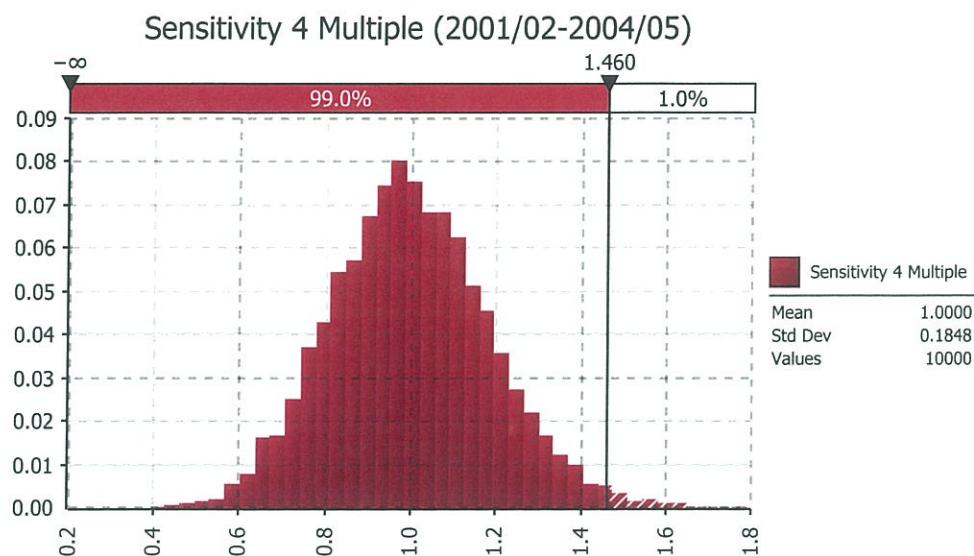


Chart 6. Distribution of Multiples, n=6

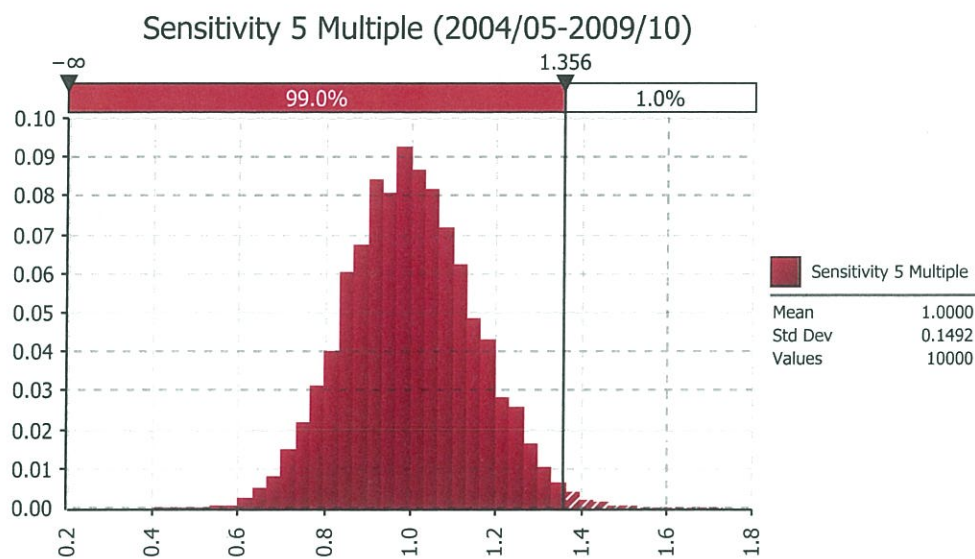


EXHIBIT C

**UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION**

)	MDL No. 2492
IN RE NATIONAL COLLEGIATE)	
ATHLETIC ASSOCIATION STUDENT-)	Master Docket No. 1:13-cv-09116
ATHLETE CONCUSSION INJURY)	
LITIGATION)	This Document Relates To:
)	All Cases
)	
)	Judge John Z. Lee
)	
)	Magistrate Judge Geraldine Soat Brown

DECLARATION OF DR. JULIAN E. BAILES

I, Dr. Julian E. Bailes, declare as follows:

1. I am the Chairman of the Department of Neurosurgery and Co-Director of the NorthShore Neurological Institute in Chicago, Illinois and a Clinical Professor of Neurosurgery at the University of Chicago Pritzker School of Medicine.

2. I am a licensed physician in the states of Illinois, Pennsylvania and West Virginia, as well as a board-certified neurological surgeon who has been either a division chief or departmental chairman for my entire career.

3. I have authored approximately 300 peer-reviewed publications, abstracts and book chapters, written five books and given nearly 500 presentations at national and international medical conferences. I also have editorial duties, serving for the last five years as Editor of Sports and Rehabilitation of the journal Neurosurgery, and I am a member of the editorial board of several journals, including the Journal of Neurotrauma.

4. Since 2002, I have been the Chairman of Sports Medicine for organized neurosurgery's two organizations, the American Association of Neurological Surgeons ("AANS") and the Congress of Neurological Surgeons ("CNS"). In 2016 I became the

Chairman-Elect of the AANS/CNS Section on Neurotrauma and Critical Care. I have been a sideline and team physician at either the National Football League (“NFL”) or the National Collegiate Athletic Association (“NCAA”) levels for the last 25 years. I am also the Chairman of the Pop Warner Football Medical Advisory Committee, which represents the oldest and largest youth football league in the United States.

5. I have received over \$27 million in research funding and maintain a basic research laboratory and supervise a research team that investigates experimental brain injury, its causes and prevention. I am the founding member and Co-Director of the Brain Injury Research Institute, which deals with issues related to the causes of chronic brain injury in sports and the military. A copy of my curriculum vitae is attached as Exhibit 1.

6. In 2001, Dr. Kevin Guskiewicz and I established the Center for the Study of Retired Athletes at the University of North Carolina, Chapel Hill, where I remain the Medical Director. My interest in the long-term effects of repetitive brain injury and cranial impacts goes back to the late 1990s, when I began, at the request of the NFL Players’ Association, to investigate the health of former professional football players, publishing data for the first time about chronic deleterious brain effects of years of football play. That work resulted in important findings, and I was a co-author of publications in 2005 and 2007 showing the incidence of cognitive impairment and depression in those retired NFL players who had three or more significant concussions.^{1,2}

¹ Ex. 2, Kevin M. Guskiewicz, et al., Association Between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players, 57 NEUROSURGERY 719, 719-26 (2005).

² Ex. 3, Kevin M. Guskiewicz, et al., Recurrent Concussion and Risk of Depression in Retired Professional Football Players, 39 MED. & SCI. IN SPORTS & EXERCISE 903, 903-09 (2007).

7. Subsequently, I began a collaboration with Dr. Bennet Omalu, who discovered Chronic Traumatic Encephalopathy (“CTE”), through which we have studied, through autopsy analysis, the brains of over 40 former football players, boxers and military veterans with CTE.³ We reported the first case of CTE in a military veteran who had been exposed to brain trauma from exposure to multiple blast injuries.⁴

8. Currently, I have been involved with the identification of CTE in living individuals, the first time that this has been shown to be possible, through positron emission tomography (“PET”) scans, in conjunction with my colleagues at UCLA.⁵

**THE VAST MAJORITY OF CONCUSSIONS RESOLVE
COMPLETELY WITH NO LONG-TERM HEALTH EFFECTS**

9. Individuals who sustain concussions may experience symptoms such as headaches, blurred vision, dizziness and concentration or memory problems.⁶ With rest, however, most concussion symptoms self-resolve in seven days.⁷ Indeed, research suggests that

³ See, e.g., Ex. 4, Bennet Omalu, et al., Emerging Histomorphologic Phenotypes of Chronic Traumatic Encephalopathy in American Athletes, 69 NEUROSURGERY 173, 173-83 (2011); Ex. 5, Bennet Omalu, et al., Chronic Traumatic Encephalopathy in an Iraqi War Veteran with Posttraumatic Stress Disorder who Committed Suicide, 31 NEUROSURGICAL FOCUS E3, at pp. 1-10 (2011).

⁴ See Ex. 5, Omalu, Chronic Traumatic Encephalopathy, supra note 3, at pp. 1-10.

⁵ See Ex. 6, Gary W. Small, et al., PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings, 21 AM. J. GERIATRIC PSYCHIATRY 138, 138-44 (2013).

⁶ See, e.g., Ex. 7, Michael A. McCrea, et al., An Integrated Review of Recovery After Mild Traumatic Brain Injury (MTBI): Implications for Clinical Management, 23 THE CLINICAL NEUROPSYCHOLOGIST 1368, 1370 (2009).

⁷ See, e.g., Ex. 8, Michael A. McCrea, et al., Standard Regression-Based Methods for Measuring Recovery After Sport-Related Concussion, 11 J. OF THE INT’L NEUROPSYCHOLOGICAL SOC’Y 58, 65 (2005) (“Less than 5% of injured athletes reported higher-than-base rate postconcussive symptoms by day 7 postinjury”); Ex. 9, Michael A. McCrea, et al., Acute Effects and Recovery Time Following Concussion in Collegiate Football Players: The NCAA Concussion Study, 290 J. OF THE AM. MED. ASS’N 2556, 2561 (2003) (“[A]pproximately 10% of players in this study required more than a week for symptoms to fully resolve.”).

approximately 90% of concussions resolve within one week of injury.⁸ For those athletes who do experience lingering symptoms, sometimes referred to as post-concussion syndrome (“PCS”), the majority of those cases resolve spontaneously or with standard medical therapy and rest, and only a small fraction continue to experience symptoms months after injury.⁹ The vast majority of student-athletes who sustain concussions have no likelihood of sustaining long-term effects from concussion.¹⁰

10. Although in recent years, some have posited the existence of possible links between concussions and long-term medical conditions such as chronic neurocognitive impairment, amyotrophic lateral sclerosis (“ALS”), Parkinsonism, Alzheimer’s disease, dementia and CTE, currently there is continued debate within the scientific community concerning the role of concussions and subsequent concussive or sub-concussive impacts, and the risks of neurodegeneration. The requisite exposure, genetic predisposition, prevalence, incidence and natural history are not yet completely understood medically and epidemiologically.¹¹ The incidence, prevalence, risk and mechanisms by which such conditions occur are not fully

⁸ See, e.g., Ex. 10, Michael A. McCrea, et al., Incidence, Clinical Course, and Predictors of Prolonged Recovery Time Following Sport-Related Concussion in High School and College Athletes, 19 J. OF THE INT’L NEUROPSYCHOLOGY SOC’Y 22, 30 (2012) (“In our study sample, 10% of injured athletes exhibited postconcussive symptoms that persisted beyond the typical seven day window of recovery commonly reported in group studies.”); Ex. 9, McCrea, Acute Effects, supra note 7, at 2561.

⁹ See, e.g., Ex. 10, McCrea, Incidence, Clinical Course, and Predictors, supra note 8, at 30 (“Nearly a quarter of those athletes who failed to meet the criteria of recovery within 1 week (2.3% of the total injured sample) continued to report elevated symptoms 6 to 12 weeks post-injury.”); id. (noting “there were no statistically significant deficits that persisted on objective neuropsychological or postural stability testing, suggesting that functional impairment 2-3 months following concussion is likely minimal” and there was “no evidence of residual impairments on performance based measures of cognitive functioning and balance 45-90 days after concussion”).

¹⁰ See, e.g., id.

¹¹ See, e.g., Ex. 11, Paul McCrory, et al., What Is the Evidence for Chronic Concussion-Related Changes in Retired Athletes: Behavioural, Pathological and Clinical Outcomes?, 47 BRITISH J. SPORTS MED. 327, at p. 4 (2013) (“At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic.”).

understood and remain the source of considerable debate.¹² Further, these conditions are largely diseases of the elderly and are extremely rare in individuals under the age of 65. Research shows that:

- Dementia, which is a significant cause of chronic neurocognitive impairment, has extremely low incidence in individuals under age 65.¹³
- ALS is a disease of the elderly, and the mean age of onset is 65.¹⁴ ALS reaches its peak incidence rate for individuals between the ages of 60 and 79 and has an extremely low incidence in individuals 40 years old and younger.¹⁵
- Parkinson's disease is a disease of the elderly and has an extremely low incidence in individuals under age 40.¹⁶ Only approximately 4% of

¹² The most significant cause of chronic neurocognitive impairment is dementia, of which there are several different types, including Alzheimer's disease, vascular dementia, and Pick's disease. See, e.g., National Institute on Aging, U.S. Dep't of Health & Human Servs., <https://www.nia.nih.gov/alzheimers/publication/dementias/types-dementia> (last visited May 17, 2016). Dementia can have many causes, however, including genetics, stroke and diabetes, and the cause of many types of dementia is unknown. See, e.g., Ex. 12, Bengt Winblad, et al., Defeating Alzheimer's Disease and Other Dementias: A Priority for European Science and Society, 15 LANCET NEUROLOGY 455, 466; 473 (2016). The causes of ALS are also unknown, but certain gene variations appear to increase the risk of ALS. See, e.g., Ex. 13, Bart Swinnen & Wim Robberecht, The Phenotypic Variability of Amyotrophic Lateral Sclerosis, 10 NATURE REV. NEUROLOGY 661, 662 (2014). Likewise, the causes of Parkinsonism are unknown, but some researchers believe it results from genetic mutations or interactions between genetic and environmental factors. See, e.g., Ex. 14, Tamara Pringsheim, et al., The Prevalence of Parkinson's Disease: A Systematic Review and Meta-Analysis, 29 MOVEMENT DISORDERS 1583, 1583 (2014); Ex. 15, Teri R. Thomsen & Robert L. Rodnitzky, Juvenile Parkinsonism: Epidemiology, Diagnosis and Treatment, 24 CNS DRUGS 467, 469-70 (2010). As with dementia, ALS and Parkinson's, the causes of Alzheimer's disease are unknown. It is believed, however, that Alzheimer's develops as a result of multiple factors rather than a single cause. See, e.g., Ex. 16, Alzheimer's Ass'n, 2015 Alzheimer's Disease Facts and Figures, 11 ALZHEIMER'S & DEMENTIA 332, 336 (2015). Risk factors include: genetic mutations; age; moderate traumatic brain injury (defined as loss of consciousness or amnesia that lasts more than 30 minutes); cardiovascular disease risk factors such as smoking, obesity and diabetes; level of education; and level of social and cognitive engagement. Id. at 336-37.

¹³ See, e.g., Ex. 12, Winblad, supra note 12, at 466 (noting "[o]lder age is the strongest risk factor for [Alzheimer's disease] and other dementias, and patients who develop dementia before age 65 years as a result of gene mutations . . . account for only a very small proportion of all cases (1-5%)"); Ex. 11, McCrory, supra note 11, at p. 2 ("The incidence of dementia (all causes) in the 30-year-old to 64-year-old group is 54/100 000.").

¹⁴ Ex. 17, M. Sabatelli, et al., Clinical and Genetic Heterogeneity of Amyotrophic Lateral Sclerosis, 83 CLINICAL GENETICS 408, 408 (2013).

¹⁵ Id. (incidence in individuals age 40 and under is 1.5/100,000 per year).

Americans diagnosed with Alzheimer's disease are younger than 65 years old, and the vast majority of Americans with Alzheimer's disease -- 81% -- are age 75 or older.¹⁷

11. Medical publications have documented that although CTE has been observed in the brains of 42 individuals who played for the National Football League, CTE has only been diagnosed in nine people who played football in college but did not go on to play after college.¹⁸ Those individuals were diagnosed pathologically. While research is ongoing to identify CTE in living individuals, a definitive diagnosis is currently only made by autopsy.¹⁹

12. Any long-term condition such as PCS would have to be diagnosed by a healthcare practitioner on a confidential basis after the concussed individual sought medical care. Such a diagnosis would remain confidential, however, unless the patient waived confidentiality and made public the diagnosis, which very few patients do.

13. Further, not every person who experiences PCS has a documented diagnosis. It is well established that a significant proportion of the U.S. population avoids seeking medical care, even when they acknowledge that doing so may be necessary.²⁰ This is true even for "individuals with major health problems or who are experiencing symptoms."²¹

(...continued)

¹⁶ Ex. 15, Thomsen & Rodnitzky, supra note 12, at 467 (incidence of 0.5/100,000 per year in individuals under the age of 40).

¹⁷ Ex. 16, Alzheimer's Ass'n, supra note 12, at 340.

¹⁸ See, e.g., Ex. 18, Joseph C. Maroon, et al., Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases, 10 PLOS ONE 1, 4 (2015).

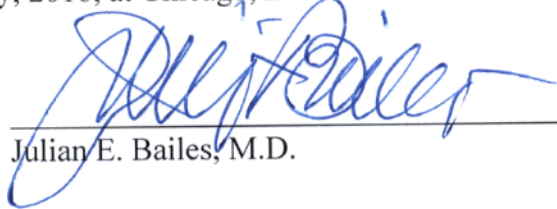
¹⁹ See, e.g., Ex. 19, Jorge R. Barrio, et al., In Vivo Characterization of Chronic Traumatic Encephalopathy Using [F-18]FDDNP PET Brain Imaging, 112 Proceedings of the National Academy of Sciences E2039, E2039 (2015) ("As with most neurodegenerative diseases, clinical diagnosis remains elusive due to the lack of specificity of CTE clinical symptomatology criteria, and histopathological examination of brain at autopsy is the most definitive diagnostic modality.").

²⁰ See, e.g., Ex. 20, Jennifer M. Taber, et al., Why Do People Avoid Medical Care? A Qualitative Study Using National Data, 30 J. GEN. INTERNAL MED. 290, 290 (2014) ("[N]early one-third of respondents in a recent national United States (U.S.) survey reported avoiding the doctor."); Ex. 21, Alexander Persoskie,

(continued...)

I declare under penalty of perjury under the laws of the state of Illinois that the foregoing is true and correct.

EXECUTED on this 19th day of May, 2016, at Chicago, Illinois.



Julian E. Bailes, M.D.

(...continued)

et al., Association of Cancer Worry and Perceived Risk with Doctor Avoidance: An Analysis of Information Avoidance in a Nationally Representative U.S. Sample, 37 J. BEHAVIORAL MED. 977, 981 (2013) (finding that 40.4% of respondents under age 50 reported avoiding visiting their doctor even when they suspected they should); Ex. 22, Viji D. Kannan & Peter J. Veazie, Predictors of Avoiding Medical Care and Reasons for Avoidance Behavior, 52 MED. CARE 336, 336 (2014) (noting “proportion of Americans forgoing or delaying needed medical care rose considerably from 2003 (14%) to 2007 (20%)”); id. at 344 (finding that although “[m]oney and time are the primary policy targets of delay related to access to care” -- e.g., the Patient Protection and Affordable Care Act -- “the most frequent responses for not seeking care were cognitive reasons”).

²¹ See, e.g., Taber, supra note 20, at 290; Ex. 23, Stephen L. Ristvedt & Kathryn M. Trinkaus, Psychological Factors Related to Delay in Consultation for Cancer Symptoms, 14 PSYCHOONCOLOGY 339, 346 (2005) (in study of patients diagnosed with rectal tumors, 17.5% waited one year or more after symptom onset before seeking medical consultation, and some individuals waited up to five years).

BAILES EXHIBIT 1

May 2016

CURRICULUM VITAE

JULIAN E. BAILES, JR. M.D.

PERSONAL

Birthplace: Alexandria, Louisiana

Address: Department of Neurosurgery
NorthShore University HealthSystem
2650 Ridge Avenue
Kellogg-3rd Floor
Evanston, IL 60201

EDUCATION

College: Louisiana State University
Baton Rouge, Louisiana
B.S. 1978

Graduate: Louisiana State University School of Medicine
New Orleans, Louisiana
M.D. 1982

Postgraduate: Externship: Neurosurgery – Head/Spinal Trauma
Los Angeles County Hospital
Los Angeles, CA
1981

Externship: Neurosurgical Oncology
Memorial Sloan Kettering Cancer Center
New York, NY
1981

Internship: General Surgery
Northwestern Memorial Hospital
Chicago, Illinois
1982-1983

Residency: Neurological Surgery
Northwestern University Medical Center
Chicago, Illinois
1983-1987

Fellowship: Cerebrovascular Surgery
Barrow Neurological Institute
Phoenix, Arizona
January-July 1988

APPOINTMENTS:

Clinical Instructor
Division of Neurosurgery
Northwestern University
Chicago, Illinois
1987

Chief, Cerebrovascular Surgery
Allegheny General Hospital
Pittsburgh, Pennsylvania
1988 - 1997

Assistant Professor
Division of Neurosurgery
Medical College of Pennsylvania
Philadelphia, Pennsylvania
1989 - 1994

Clinical Instructor
Department of Neurosurgery
West Virginia University
Morgantown, West Virginia
1989 - 1993

Clinical Assistant Professor
Department of Neurosurgery
West Virginia University
1993 - 1997

Associate Professor
Division of Neurosurgery
Medical College of Pennsylvania/Hahnemann Univ.
Philadelphia, Pennsylvania
1994 - 1997

Senior Vice President
Medical Director
Orlando Regional Healthcare System
CareLink Management
Orlando, Florida
1997 - 1998

President/CEO
Greater Orlando Neurosurgery & Spine, P.A.
Orlando, Florida
1998 - 2000

Medical Director
Emergency Medical Services
Osceola County, Florida (Greater Metropolitan Orlando, selected by County Commission)
1998 - 2000

Director, Neurosurgery
Disneyworld Celebration Hospital
Orlando, Florida
1999 - 2000

Assistant Professor, College of Health and Public Affairs
University of Central Florida
Orlando, Florida
1999 - 2000

Professor and Chairman, Department of Neurosurgery
West Virginia University School of Medicine
Morgantown, WV
2000 –2011

Bennett Tarkington Chairman
Department of Neurosurgery
Co-Director, NorthShore Neurological Institute
NorthShore University Health System
Clinical Professor of Neurosurgery
University of Chicago Pritzker School of Medicine
Evanston, IL
2011-present

Co-Chairman, West Virginia Governor's Task Force on Healthcare
2005

Chairman, West Virginia Health Information Network
2006 to 2011

Chairman, Sports Medicine Committee, American Association of Neurological Surgeons & Congress of Neurological Surgeons 2002 to present

Advisor, NFL Players Association Committee on Head Injuries, 2007 to present

NASA Crew Protection Work Group, Orion Mars-Lunar Mission, Houston, TX, 2007-2009

Advisor, Competitive Safeguards & Medical Aspects of Safety Committee, NCAA, 2009 to present

Board of Directors, Blanchette Rockefeller Neurosciences Institute, 2009 to 2011

Medical Director, Spokesman, Progesterone for severe TBI, FDA-approved study, BHR Pharma, 2010-2011.

Chairman, Medical Advisory Board, Pop Warner Football, Inc. Philadelphia, PA. 2010 to present

Director, NFL Players Association, Second Opinion Network. 2010 to present

Neurological Consultant, NCAA

Neurological Consultant, Southeastern Conference

Neurological Consultant, National Federation of High Schools

Neurological Consultant, Arena Football League

Board of Directors, Chicago Interurban Neurosurgical Society, 2013 to present

Secretary/Treasurer, American Association of Neurological Surgeons/Congress of Neurological Surgeons Section Neurotrauma and Critical Care, 2014 to present. Chairman, 2018-2020.

AWARDS

Outstanding Radiology Student, Louisiana State University School of Medicine
New Orleans, Louisiana, 1982.

Anne Addington Research Award, Northwestern University, Chicago, Illinois, 1984.

Health Hero Award for Healthcare Innovations in Pennsylvania, Pittsburgh Business Times, Pittsburgh, 1996. (Telemedicine)

Outstanding Healthcare Achievement of 1996, Pittsburgh Executive Report Magazine 1996.
(Telemedicine)

Finalist, Cerebral Resuscitation Project Competition, National Association of Emergency Medical Physicians, 1996. "Hypothermic Blood Substitutes to Resuscitate from Hemorrhagic Shock."

Dean's Excellence Award for Clinical Service, West Virginia University School of Medicine. 2001, 2003.

Leica Visionary in Neurosurgery Award, 2004.

"America's Best Doctors" 2001-02, 2003-04, 2005-06, 2007-08, 2009-10. 2011, 2012, 2013.

"America's Top Surgeons" 2006, 2007, 2009, 2010, 2011, 2012, 2013.

Louisiana State University Hall of Distinction Inductee 2011 (highest university honor granted to alumnus).

"Chicago Top Neurosurgeons", Chicago Magazine 2014.

"Healthcare Hero Award" The Association of Boxing Commissions Medical Committee Annual Meeting, Clearwater Beach, FL. July 28, 2014.

Inductee to the Louisiana Sports Hall of Fame and recipient of the Dave Dixon Louisiana Sports Leadership Award, June 23, 2016.

MEDIA APPEARANCES

ESPN, NBC Sports, Good Morning America, CNN, CNN Sports, Anderson Cooper Show, CBS Morning Show, Outside the Lines, C-Span, Today Show, NBC Nightly News, Larry King Live, PBS, Dr. Oz Show, ABC Nightline, ABC Secrets of Your Mind mini-series, ESPN Magazine, Al Jazeera, Northwest Herald, Time, Sports Illustrated, and various local media.

GRANTS – Principal or Co-Investigator

1986	Study of Effects of CO2 Laser on Primate Peripheral Nerves	Marshall Bennett Fund, Evanston Hospital, Evanston, IL	1986\$30,000
1989	Study of Ultraprofound Hypothermia with blood substitution in canine model	Allegheny-Singer Research Institute, Pittsburgh, PA	\$5,000
1989	Study of effects of hypothermia and blood substitution in multiorgan systems	Cryomedical Sciences, Inc., Washington, D.C.	\$1,000,000
1993	Shock trauma model of hypothermia and blood substitution	Cryomedical Sciences, Inc., Bethesda, MD	\$135,000
1993	Cardiac effects of intracranial hemorrhage	Allegheny-Singer Research Institute, Pittsburgh, PA	\$10,000
1995	National Medical Practice Knowledge Bank, NIST-ATP Grant No. 70NANB5H1183	U.S. Department of Commerce	\$21,300,000
1995	Tirilizad In Subarachnoid Hemorrhage, Principal Investigator	Upjohn, Inc	\$600,000
1996	Telemedicine for Rural Health Care Delivery, Clinical Principal Investigator	U.S. Department of Commerce	\$450,000
1996	Hypothermia and Blood Substitution - Canine and Primate Models, \$100,000	Allegheny-Singer Research Institute	\$100,000
1997	Head Injuries in Professional Football Players, annual to present	NFLPA Players Association	\$135,000
1999	National Center for Study of Concussion in NFL Players	Celebration Health	\$5,000
1999	Teaching Models of Cardiac Cerebral and Trauma Resuscitation	Osceola County Fire-Rescue Service	\$15,000
2003	Medical Models of Homeland Security	Conaway Group	\$25,000
2004	NFL Players' Association Center for Study of Retired NFL Athletes	Medtronic, Inc.	\$250,000
2004	Homeland Security Comprehensive Assessment Model	U.S. Department of Homeland Security	\$700,000
2005	Skull Base Lab Research	Synthes, Inc.	\$30,000
2006	Omega 3 Fatty Acids in Traumatic Brain Injury	Inflammation Research Foundation	\$30,000
2006	Skull Base Lab Research	Synthes, Inc.	\$30,000
2007	Omega 3 Fatty Acids for Traumatic Brain Injury	Martek, Inc.	\$30,000
2007	WVU Neurosurgical Chair	Hazel Ruby McQuain Foundation	\$1,500,000
2007	DHA Supplementation for Prevention of Cognitive Deficits in Retired NFL Players	Martek, Inc.	\$350,000
2007	Skull Base Lab Research	Synthes, Inc	\$30,000
2008	WV State-wide Stroke Network	Hazel Ruby McQuain Foundation	\$300,000
2008	DHA Pre-Treatment for TBI	Martek, Inc.	\$76,000
2008	Skull Base Lab Research	Synthes, Inc	\$30,000
2009	Skull Base Lab Research	Synthes, Inc	\$30,000
2010	Progesterone	BHR Pharma	\$61,000
2013	Concussion Models/Treatment	Abbott Laboratories	\$135,000
2014	TBI Large Animal Model	Q30 Labs	\$66,300
Total Grant Funding			27,458,300

MEMBERSHIPS

American Medical Association
Congress of Neurological Surgeons
American Association of Neurological Surgeons
Pennsylvania Medical Society
Allegheny County Medical Society
Society of Cryobiology
Research Society of Neurological Surgeons
Joint Section AANS/CNS Neurotrauma and Critical Care
Joint Section AANS/CNS Cerebrovascular Surgery
Neurosurgeons for Health Care Reform
Aequanimitas Neurosurgical Society, President
Executive Council, Joint Section AANS/CNS for Trauma & Critical Care
Executive Council, AANS/CNS Joint Section of Cerebrovascular Surgery
West Virginia State Medical Association
American College of Emergency Physicians
Monongalia County Medical Society
West Virginia Emergency Medical Services Council

ADMINISTRATIVE (Institutional and Clinical)

Medical Director, Allegheny General Hospital Telemedicine
Medical Director, Neurolink Telemedicine
Medical Director, Allegheny Physician Access
Chairman, AHERF Committee on Telemedicine
Neurosurgical Consultant, Pittsburgh Steelers Football Team 1988 to 1997
Chairman, Neurosurgical ICU Critical Care Committee 1988 - 1991
Medical Advisory Board, E-Systems Medical Electronics
Neurosurgical Consultant, University of Central Florida, 1998-99
Florida Association of Emergency Medical Services Directors
Medical Director, Carelink Management Nursing Homes and Home Health Care Agency, Orlando, FL 1997-98
Carelink Advisor for Care Utilization, Prescription Drugs, Medicare Regulations. 1997-98
Medical Director, Center for Study of Head Injuries in Professional Athletes, University of North Carolina, Chapel Hill
Medical Director, Emergency Medical Services, Ocala County, Florida. 1998-2000
Medical Director, Emergency Medical Services, City of Kissimmee, Florida 1998-2000
Medical Director, Emergency Medical Services, City of St Cloud, Florida 1998-2000
Medical Advisor, Orange Co FL Sheriff's Office and National Sheriffs Association
Medical Director, National Domestic Preparedness Partnership (WVNG, WVSP) 2002-Present
Medical Advisor, Joint Agency Anti-Drug Task Force, Region Five WV 2002-Present
Medical Advisor, West Virginia State Police 2002-2011
Medical Director, Homeland Security Comprehensive Assessment Model, Orange County, FL, 2002-Present
Chairman, Sports Medicine AANS/CNS Section on Trauma, 2005-present

National Task Force for Transport of Injured Athletes
Examiner, American Board of Neurological Surgeons, 2000, 2004, 2010
Medical Review Committee, Association of Boxing Commissions, 2010
Chairman-Elect, AANS/CNS Joint Section on Trauma and Critical Care 2016

NATIONAL / INTERNATIONAL

Program Chairman, AANS/CNS Joint Section of Cerebrovascular Surgery, AANS Meeting Apr, 1996
Program Director: Sports Related Concussion and Nervous System Injury. Orlando, FL, Feb, 1997
Program Director: Sports Related Concussion and Nervous System Injury, Orlando, FL, Mar, 1988
Program Director: Sports Related Concussion and Nervous System Injury, Orlando, FL, May 1999
Scientific Committee, Joint Section on Cerebrovascular Surgery, Annual Meeting, Orlando, FL, Feb, 1998
Chairman, Internet Access Committee, Congress of Neurological Surgeons Annual Meeting, New Orleans, LA September, 1997
Cerebrovascular Section Representative to "Neurosurgery On-Call", Internet Access
Chairman, Scientific Advisory Committee, Cryomedical Sciences, Inc.
Chairman, Host Committee, 1991 Congress of Neurological Surgeons
Chairman, Videotape Library, 1992 Congress of Neurological Surgeons
Chairman, Steering Committee on Telemedicine, AHERF
Chairman, Medical Advisory Committee, NMPKB project
Member, State Trauma System Action Team, Charleston, WV, 2002
President, West Virginia Neurosurgical Society, 2002-Present
President, Neurosurgical Society of The Virginias, 2004-2006

EDITORIAL

Editor, Neurosurgery (2009 to 2014)
Editorial Board, Journal of Neurotrauma
Editorial Board, Computerworld, (1996-1997)
Editorial Board, Telemedicine and e-Health (2002 – present)
Editorial Board, Neurosurgery On-Call (1996-2002)
Editorial Board, CNS/AANS Videotape Library (1989-1993)
Editor, Allegheny General Hospital Neuroscience Journal (1989-1993)
Editorial Board, Journal of Reconstructive Microsurgery Romania (1996-2002)
Editorial Board, AANS/CNS Publications Committee (1996-1999)
Reviewer, Neurosurgery
Reviewer, Journal of Neurotrauma
Reviewer, Stroke
Reviewer, American Journal of Sports Medicine
Reviewer, Journal of Orthopaedic and Sports Physical Therapy
Reviewer, Sports Medicine (Australia)
Reviewer, Athletic Training
Reviewer, Physician and Sports Medicine
Reviewer, Canadian Medical Journal
Reviewer, Zentralblatt für Neurochirurgie
Reviewer, PLOS one

LICENSURE

State	Year	Cert. No.
Louisiana	1982	016562
Illinois	1984	069762-1
Arizona	1988	17274
Pennsylvania	1988	041673E
Ohio	1996	35-07-1901
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CERTIFICATION

American Board of Neurological Surgery

Certificate No.	92062
Written Passed	1986
Oral Passed	1992

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CHAPTERS

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128. Bailes JE: Surgical treatment of stroke. Grand Rounds, Somerset Hospital, Somerset, PA, October 1992.
129. Leavitt ML, Bailes JE, Shih SR, Taylor MJ, Elrifai AM, Teeple E, Maroon JC, Devenyi C, Ciongoli K, Bazmi B: Brain versus body temperature changes after profound hypothermic cardiac arrest. Soc Neuroscience, Anaheim, CA, October 1992.
130. Elrifai AM, Bailes JE, Teeple E, Leavitt ML, Shih SR, Taylor MJ, Maroon JC: Serum levels of creatinine kinase (CK) in hypothermia and complete blood substitution. Soc Neuroscience, Anaheim, CA, October 1992.
131. Bailes JE: Vascular relationships of the terminal basilar artery. AGH Neuroscience Journal, Fall 1992.
132. Bailes JE, Vidovich D: Comprehensive approach for repairing basilar artery apex aneurysms. AGH Neuroscience Journal, Fall 1992.
133. Teeple E, Elrifai AM, Bailes JE, Shih SR, Leavitt ML, Taylor MJ, Maroon JC, Ciongoli KA, Devenyi C, Bazmi B: A summary of the means of support required during resuscitation from profound hypothermia and complete blood substitution. Int Soc Appl Cardiovasc Biology, St. Louis, MO, November 1992.
134. Leavitt ML, Bailes JE, Shih SR, Taylor MJ, Elrifai AM, Teeple E, Maroon JC: Low flow extracorporeal circulation in totally blood substituted profoundly hypothermic dogs. Int Soc Appl Cardiovasc Biology, St. Louis, MO, November 1992.
135. Bailes JE: Cerebral aneurysms. Dubois Regional Medical Center Staff Conference, Dubois, PA, January 1992.
136. Leavitt ML, Bailes JE, Elrifai AM, Taylor MJ, Teeple E, Shih SR, Maroon JC: Asanguineous perfusion of profoundly hypothermic dogs: An update. An Meet American Academy of Cardiovascular Perfusion, San Antonio, TX, January 1993.
137. Bailes JE: surgical treatment of stroke. Medical Staff Conf. Armstrong Memorial Hospital, Kittanning, PA, March 1993.
138. Leavitt ML, Bailes JE, Taylor MJ, Shih RS, Elrifai Am, Teeple E, Maroon JC: Motor activity during rewarming subsequent to profound hypothermic cardiac arrest in totally blood substituted dogs. An Meet Fed Amer Soc Exp Biol. New Orleans, LA, March 1993.
139. Elrifai AM, Bailes JE, Teeple E, Shih SR, Taylor MJ, Leavitt ML, Maroon JC: Cerebral perfusion pressure in profound hypothermic cardiac arrest in canines. Int Anesth Res Soc, San Diego, CA, March 1993.
140. Bailes JE: Surgical treatment of stroke. Medical Staff Meeting, Sharon General Hospital, Sharon, PA, April 1993.
141. Bailes JE: Head injuries in athletes. American Assoc. Neurological Surgeons, Boston, MA, April 1993.
142. Maroon JC, Bailes JE, Quigley MR, Wilberger JE, Onik G: Cryosurgical application in the treatment of brain, spinal and orbital tumors. American Assoc Neurological Surgeons, Boston, MA, April 1993.

143. Bailes JE: Cervical spine trauma in athletes. Pennsylvania Athletic Trainers' Society. Hershey, PA, May 1993.
144. Bailes JE: Recognizing and managing cranial trauma in athletes. Pennsylvania Medical Trainers' Society. Hershey, PA, May 1993.
145. Elrifai AM, Bailes JE, Govindan S, Leavitt ML, Teeple E, Shih SR, Taylor MJ, Adatepe MH, Maroon JC: Evaluation of cerebral blood flow using radioactive Xenon133 pre vs post-hypothermia and blood substitution. Int Meet Cereb Blood Flow Metabol. Sendai, Japan, May 1993.
146. Bailes JE: Intraoperative angiography and temporary balloon occlusion of the basilar artery. International Congress on Minimally Invasive Techniques in Neurosurgery. Weisbaden, Germany, June 1993.
147. Taylor MJ, Elrifai AM, Bailes JE, Shih SR, Teeple E, Leavitt ML, Maroon JC, Ciongoli KA, Devenyi C: The use of aqueous blood substitution during 3 hours of experimental hypothermic cardiac arrest. Fifth Eur Cong Extra-Corporeal Technol, Arles, France, June 1993.
148. Taylor MJ, Bailes JE, Elrifai AM, Shih SR, Teeple E, Leavitt ML, Baust JG, Maroon JC: New aqueous blood substitutes for general tissue preservation during 3 hours of profound hypothermic cardiac arrest: I. Solution design and biochemical outcome. CRYO 93, An Meet Cryobiology Soc, Atlanta, GA, July 1993.
149. Elrifai AM, Bailes JE, Taylor MJ, Teeple E, Shih SR, Leavitt ML, Baust JG, Maroon JC: New aqueous blood substitutes for general tissue preservation during 3 hours of profound hypothermic cardiac arrest: I. Methods and Neurological Outcome. CRYO 93, An Meet Cryobiology Soc, Atlanta, GA, July 1993.
150. Elrifai AM, Bailes JE, Maroon JC, Shih SR, Taylor MJ, Teeple E, Leavitt ML, Ciongoli KA: The correlation of rewarming with outcome in an experimental canine model of profound hypothermia involving blood substitution and cardiac arrest. CRYO 93, An Meet Cryobiology Soc, Atlanta, GA, July 1993.
151. Elrifai AM, Bailes JE, Teeple E, Taylor MJ, Shih SR, Leavitt ML, Maroon JC: Monitoring cerebral perfusion pressure in experimental profound hypothermia and cardiac arrest. CRYO 93, An Meet Cryobiology Soc, Atlanta, GA, July 1993.
152. Bailes JE: Perioperative management of subarachnoid hemorrhage. Congress of Neurological Surgeons, Vancouver, BC, October 1993.
153. Bailes JE, Elrifai AM, Taylor MJ, Shih SR, Teeple E, Leavitt ML, Baust JG, Maroon JC: Ultra-profound hypothermia combined with blood substitution: A new protocol for extending the safe limits of cardiac arrest up to 3 hours. Am Coll Surgeon, Surg Forum An Meet, San Francisco, CA, October 1993.
154. Elrifai AM, Bailes JE, Govindan S, Teeple E, Taylor MJ, Shih SR, Leavitt ML, Adatepe MH, Maroon JC: Evaluation of cerebral blood flow using radioactive Xenon133 after long term survival of animals exposed to profound hypothermia and complete blood substitution. An Meet Soc Neuroscience, Washington, DC, November 1993.
155. Bailes JE: Characterization of cardiac rhythm and contractility abnormalities following

subarachnoid hemorrhage in canine model. Aequanimitas - Kasdon Winter Meeting, Jackson Hole, WY, March 1994.

156. Bailes JE: Management of athletic head and spinal injuries. Neurological Injuries in Sports Medicine Conference, Orlando, FL, March 1994.
157. Bailes JE: Management of head and spinal "spear" injuries in athletes. American Association of Neurological Surgeons, San Diego, CA, April 1994.
158. Bailes JE, Elrifai AM, Shih SR, Maroon JC, Nellis K: Characterization of the cardiac rhythmic and myocardial disturbances that occur following experimentally induced subarachnoid hemorrhage. American Association of Neurological Surgeons, San Diego, CA, April 1994.
159. Bailes JE: Skull base approaches to intracranial aneurysms. ANI Mini Symposium in Skull Base Surgery, Pittsburgh PA, April 1994.
160. Taylor MJ, Bailes JE, Elrifai AM, Shih SR, Teeple E, Leavitt ML, Baust JG, Maroon JC: Cellular protection using new hypothermic blood substitutes during 3 hr cardiac arrest. American Society for Artificial Internal Organ Ann Meet, San Fransisco, CA, April 1994.
161. Elrifai AM, Bailes JE, Teeple E, Taylor MJ, Shih SR, Leavitt ML, Maroon JC: Monitoring cerebral perfusion pressure in experimental profound hypothermia and cardiac arrest. Advances in Clinical Aspects of Cerebral Blood Flow Conference, Pittsburgh, PA, April 1994.
162. Elrifai AM, Bailes JE, Gobindan S, Teeple E, Taylor MJ, Shih SR, Leavitt ML, Adatepe MH, Maroon JC: Evaluation of cerebral blood flow using radioactive Xenon133 after long term survival of animals exposed to profound hypothermia and complete blood substitution. Advances in Clinical Aspects of Cerebral Blood Flow Conference, Pittsburgh, PA, April 1994.
163. Elrifai AM, Bailes JE, Diamond DL, Taylor MJ, Simon D, Davis D, Shih SR, Clark RE, Maroon JC: Hemorrhagic shock model of profound hypothermia and complete blood substitution: Transcranial carotid doppler evaluation of cerebral blood flow velocity. Advances in Clinical Aspects of Cerebral Blood Flow Conference, Pittsburgh, PA, April 1994.
164. Taylor MJ, Bailes JE, Elrifai AM, Shih SR, Baust JG, Maroon JC: New approaches to bloodless surgery using complete blood substitution and profound hypothermia. Invited paper at International Resuscitation Research Conference, University of Pittsburgh, Pittsburgh, PA, May 1994.
165. Bailes JE: Minor head injury in athletes. National Athletic Trainers Assoc. Symposium, Washington, DC, June 1994.
166. Bailes JE, Fukushima T: Surgical strategies for paraclinoid giant aneurysms. 6th Annual Meeting Japanese Skull Base Society, Nagoya, Japan. June 1994.
167. Bailes JE: Present and future applications of profound hypothermia in skull base surgery. 6th Annual Meeting Japanese Skull Base Society, Nagoya, Japan. June 1994.
168. Taylor MJ, Simon D, Elrifai AM, Shih SR, Bailes JE, Maroon JC, Diamond DL: A feasibility study in a canine model for using profound hypothermia and blood substitution with Hypothermosol to enable resuscitation after hemorrhagic shock. Ann Meet Soc of Cryobiology, Japan, August 1994.

169. Bailes JE: Treatment options for the acute stroke patient. Grand Rounds, Somerset Hospital, Somerset, PA, August 1994.
170. Taylor MJ, Bailes JE, Elrifai AM: Hypothermia and blood substitution. Research Institute for Brain and Blood Vessels, Akita, Japan, August 1994.
171. Bailes JE: Treatment options for the acute stroke patient: Grand Rounds, Elk County Hospital, Ridgeway, PA, September 1994.
172. Bailes JE: Medical triage using a new telemedicine system: NeuroLink. Charles Cole Memorial Hospital, Coudersport, PA, September 1994.
173. Bailes JE: NeuroLink: A computerized neurosurgical telemedicine network. Sharon Regional Medical Center Grand Rounds, Sharon, PA, September 1994.
174. Bailes JE: Surgical treatment of cerebral aneurysms and care of the subarachnoid hemorrhage patient. Medical Grand Rounds, Shadyside Hospital, Pittsburgh, PA, September 1994.
175. Elrifai AM, Bailes JE, Teeple E, Taylor MJ, Shih SR, Maroon JC: Monitoring cerebral perfusion pressure in experimental profound hypothermia and cardiac arrest. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
176. Elrifai AM, Bailes JE, Diamond DL, Taylor MJ, Simon D, Davis D, Shih SR, Clark RE, Maroon JC: Hemorrhagic shock model of profound hypothermia and complete blood substitution: Transcranial carotid doppler evaluation of cerebral blood flow velocity. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
177. Elrifai AM, Bailes JE, Maroon JC, Shih SR, Taylor MJ, Teeple E: The correlation of rewarming with outcome in an experimental canine model of profound hypothermia involving blood substitution and cardiac arrest. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
178. Elrifai AM, Bailes JE, Maroon JC, Shih Sr, Teeple E, Taylor MJ: Brain temperature in profound hypothermia: An experimental observation. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
179. Taylor MJ, Elrifai AM, Shih SR, Bailes JE, Maroon JC: A feasibility study in a canine model for using profound hypothermia and blood substitution with Hypothermosol to enable resuscitation after hemorrhagic shock. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
180. Elrifai AM, Bailes JE, Teeple E, Shih SR, Taylor MJ, Maroon JC: Serum levels of creatinine kinase (CK) in hypothermia and complete blood substitution. International Symposium on Hypothermic Medicine, Pittsburgh, PA, September 1994.
181. Bailes JE: Surgical approaches to basilar trunk and vertebrobasilar aneurysms. Annual Meeting Congress of Neurological Surgeons. Chicago, IL, October 1994.
182. Bailes JE, Maroon JC: Preliminary experience and cost analysis with NeuroLink: A neurosurgical wide area computer network. Annual Meeting Congress of Neurological Surgeons, Chicago, IL, October 1994.
183. Bailes, JE, Elrifai AM, Taylor MJ, Maroon JC, Shih SR: Ultraprofound hypothermia with blood

substitution in a shock trauma model. Annual Meeting Congress of Neurological Surgeons, Chicago, IL, October 1994.

184. Elrifai AM, Bailes JE, Govindan S, Teeple E, Taylor MJ, Shih SR, Adatepe MH, Maroon JC: Cerebral blood flow measurement using radioactive Xenon 133 under Pentothal and Fentanyl Anesthesia. Ann Meet Soc Neuroscience, Miami, FL, November 1994.
185. Bailes JE: Surgical approaches to vertebrobasilar junction and basilar trunk aneurysms. ANI Annual Cerebrovascular Symposium, Pittsburgh, PA, December 1994.
186. Bailes JE: Skull base approaches to cerebral aneurysms. Pan-Pacific Skull Base Surgery Workshop, Lanai, Hawaii, March 1995.
187. Elrifai AM, Bailes JE, Taylor MJ, Simon D, Shih SR, Govindan S, Diamond D: Transcranial carotid doppler evaluation of cerebral blood flow velocity in a hemorrhagic shock model of profound hypothermia and complete blood substitution. Ann Meet Am Soc Neuroimaging, San Juan, Puerto Rico, March 1995.
188. Bailes JE: Surgical treatment of stroke. Sharon Regional Health System, Sharon, PA, March 1995.
189. Elrifai AM, Taylor MJ, Bailes JE, Shih SR, Wilberger JE, Maroon JC: A new hypothermic preservation solution for neural tissue preservation. Am Soc Neural Transpl, Tampa, FL, April 1995.
190. Bailes JE: Neurological injuries and the athlete. Amer Assoc Neurol Surgeons. Orlando, FL, April 1995.
191. Bailes JE: Traumatic head and neck injuries. Sports Medicine Update, Dept of Orthopedics, Allegheny General Hospital, Pittsburgh, PA, May 1995.
192. Simon D, Taylor MJ, Elrifai AM, Shih SR, Bailes JE, Davis D, Kluger Y, Diamond D: Profound hypothermia and blood substitution enables resuscitation after hemorrhagic shock. American Society for Artificial Internal Organ Ann Meet, Chicago, IL, May 1995.
193. Bailes JE: Ultraprofound hypothermia. Joint International Congress on Minimally Invasive Techniques in Neurosurgery and Otolaryngology, Pittsburgh, PA, June 1995.
194. Bailes JE: Implementation of telemedicine networks for neurosurgical care. Neurosurgical Society of America, Sea Island, GA, June 1995.
195. Bailes JE: Surgical strategies for giant paraclinoid aneurysms. 4th International Workshop on Cerebrovascular Surgery, Chicago, IL, June 1995.
196. Bailes JE: Future advances in application of blood substitution and ultraprofound hypothermia for cerebrovascular surgery. 4th International Workshop on Cerebrovascular Surgery, Chicago, IL, June 1995.
197. Bailes JE: Stroke prevention and treatment. Armstrong County Memorial Hospital, Kittanning, PA, June 1995.
198. Bailes JE: Current and future prospects of telemedicine systems in neurological surgery. Aequanimitas Annual Meeting, Jackson Hole, WY, July 1995.

199. Bailes JE, Elrifai AM, Taylor MJ, Shih SR, Simon D, Diamond D: Combining ultra-profound hypothermia with blood substitution facilitate resuscitation from hemorrhagic shock. Am Coll Surgeon, Ann Meet, New Orleans, LA, October 1995.
200. Bailes JE: Principles and procedures in neuromonitoring for intracerebral and cerebrovascular surgery. Principles and Applications of Intraoperative Neurophysiologic Monitoring. Pittsburgh, PA November 1995.
201. Bailes JE: Skullbase approaches to intracranial aneurysms. ANI Second Annual Cerebrovascular Symposium. Pittsburgh, PA December 1995.
202. Dianzaumba SB, Bailes JE, Elrifai AM, Shih SR, Emory R, Maroon JC and Reichek N. Intracranial hemorrhage induces cardiac damage. 68th Ann meeting, Am Heart Association, Anaheim, CA, November 1995.
203. Taylor MJ, Bailes JE, Elrifai AM, Shih SR, Simon D, Diamond DL, Maroon JC: Design and evaluation of hypothermic blood substitutes to facilitate resuscitation after hemorrhagic shock and 2 hr of cardiac arrest in canines. NAEMSP, Naples, FL January 1996.
204. Bailes JE: Update on the management of carotid artery disease. AGH Medical Grand Rounds, Pittsburgh, PA, January 1996.
205. Bailes, JE: Design and Evaluation of Hypothermic Blood Substitutes to Facilitate Resuscitation after Neurologic Shock and 2 hr. of Cardiac Arrest in Canines. National Assoc. EMS Physicians, Naples, FL, January 1996 (Finalist-Cerebral Resuscitation Papers).
206. Bailes, JE: Techniques of Carotid Endarterectomy. St. Louis University, Practical Anatomy Workshops, St. Louis, MO, January 1996.
207. Bailes, JE: Thrombotic and Embolic Complications of Carotid Endarterectomy. AHA Stroke Meeting, Cerebrovascular Section, San Antonio, TX, January 1996.
208. Bailes, JE: Surgical Management of Complex Cerebral Aneurysms. Update on Cerebral Aneurysm Conference. BroMenn Medical Center, Bloomington, Ill., February 1996 (Invited Guest).
209. Bailes, JE: Telemedicine Program in AHERF. Neuroscience Grand Rounds, AGH, Pittsburgh, PA February 1996
210. Bailes, JE: Neurosurgical Management of Head Injuries in Athletes. Conference on Sports Related Concussion, Pittsburgh, March 1996.
211. Bailes, JE: Hypothermia Applications in Neurosurgery. International Winter Congress on Minimally Invasive Techniques in Neurosurgery and Otolaryngology, Aspen, CO March 1996.
212. Bailes, JE: Minimally Invasive Techniques Applied to Carotid Artery Surgery. International Winter Congress on Minimally Invasive Techniques in Neurosurgery and Otolaryngology, Aspen, CO, March 1996.
213. Bailes, JE: Assessment and Management of patients with symptomatic and asymptomatic carotid stenosis. New Dimensions in Cardiology for the Primary Care Physician. Pittsburgh, PA March 1996.

- 214. Bailes, JE: Experimental Hypothermia. 16th Annual Meeting of Japanese Society of Neurological Surgeons. Matsue, Japan, April 1996 (Invited Guest).
- 215. Bailes, JE: Carotid Endarterectomy. 16th Annual Meeting of Japanese Society of Neurological Surgeons. Matsue, Japan, April 1996 (Invited Guest).
- 216. Bailes, JE: Thoracolumbar Injuries in Athletes. AANS Annual Meeting. Minneapolis, MN, April 1996.
- 217. Bailes, JE: Brachial Plexus Injuries in Athletes. AGH Sports Medicine Symposium. Pittsburgh, PA April 1996.
- 218. Bailes, JE: Overview of Skull Base Procedures in Cerebral Aneurysm Surgery and Moderator, Joint Section of Cerebrovascular Surgery, AANS Annual Meeting, Minneapolis, MN April 1996.
- 219. Bailes, JE: Brain attack protocol at AGH. Sharon Regional Health Center, Sharon, PA May 1996.
- 220. Bailes, JE: Design and implementation of a neurosurgical wide area network. Telemedicine 2000, Chicago, IL May 1996.
- 221. Bailes, JE: Assessment of cumulative head injury in professional football players. NFL Players Assoc. Annual Meeting, Albuquerque, NM, April 1996.
- 222. Bailes, JE: Controversial Problems in Athletes with Spinal Abnormalities. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 223. Bailes, JE: New Therapeutic Strategies for the Management of Head Injuries. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 224. Dureza C, Bailes JE, Maroon JC: A Preliminary Report on the Use of the Procap in Full Contact Football. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 225. Dureza C, Fukushima T, Bailes JE, Kiya N, Maroon JC: Minimally Invasive Endoscopic Carotid Endarterectomy. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 226. Dureza C, Fukushima T, Bailes JE, Levy DI, Maroon JC: The Use of Titanium VCS Autosuture in Cerebrovascular Surgery. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 227. Bailes JE, Tantuwaya L, Fukushima T: Intraoperative Microvascular Doppler Sonography in Aneurysm Surgery. Congress of Neurological Surgeons, 46th Annual Meeting, Montreal, Canada, Sept. 1996.
- 228. Bailes JE: Construct and deployment of wide area neurosurgical network. National Medical Practice Knowledge Bank Symposium, Pittsburgh, PA Dec. 1996.
- 229. Bailes JE: Complications of carotid artery surgery. Joint Section on Cerebrovascular Surgery Annual Meeting, Anaheim, CA, February 1997.
- 230. Bailes JE: Selected cases of carotid artery origin cerebral ischemia management options. Joint

Section on Cerebrovascular Surgery Annual Meeting, Anaheim, CA, February 1997.

- 231. Medary M, Bailes JE: EEG is the most reliable indicator for intraluminal shunting during carotid endarterectomy. Joint Section on Cerebrovascular Surgery Annual Meeting, Anaheim, CA, February 1997.
- 232. Bailes JE: Neurosurgical management of athletic head injuries. Sports related concussion and nervous system injuries. Orlando, FL, February 1997.
- 233. Bailes JE: Overview of athletic spine and spinal cord injuries. Sports related concussion and nervous system injuries. Orlando, FL February 1997.
- 234. Bailes JE: Evolution of telemedicine and application to a national medical knowledge bank. Neuroscience Conference, Allegheny General Hospital, Pittsburgh, PA February 1997.
- 235. Bailes JE: Development and implementation of a neurosurgical wide area network. Implications of an internet based system. Neurosurgical Society of America, Annual Meeting. London, March 1997.
- 236. Bailes JE: Injuries of the cervical spine, spinal cord, and peripheral nerves in athletes, Amer. Assoc. Neurol Surg., Annual Meeting, Denver, CO, April 1997.
- 237. Bailes JE: Head injuries in athletes. American Medical Society for Sports Medicine, Annual Meeting, Colorado Springs, CO, April 1997.
- 238. Bailes JE: Future telemedicine systems in neurosurgery. Southern Neurosurgical Society Ann. Meeting. Pinehurst, NC., May 1997.
- 239. Bailes JE: Critical care aspects of athletic nervous system injuries. Congress of Neurological Surgeons Ann. Meeting, New Orleans, LA., Sept. 1997.
- 240. Bailes JE: Anatomical and operative aspects of carotid endarterectomy. Congress of Neurological Surgeons Ann. Meeting, New Orleans, LA., Sept. 1997.
- 241. Bailes JE: Overview and classification of sports medicine for the neurosurgeon. Congress of Neurological Surgeons Ann. Meeting, New Orleans, LA., Sept. 1997.
- 242. Bailes JE: The National Medical Practice Knowledge Bank Project. Congress of Neurological Surgeons Ann. Meeting, New Orleans, LA., Sept. 1997.
- 243. Bailes JE: Computerized systems and Telecommunications: Present and Future Technology. Congress of Neurological Surgeons Ann. Meeting, New Orleans, LA., Sept. 1997.
- 244. Bailes JE: Webmedicine, The Internet and message management for future medicine. Telehealth and the Business of Telemedicine Meeting, Denver, CO., October 1997.
- 245. Bailes JE: Neurological telemedicine, Telemedicine 2000, Orlando, FL., Nov. 1997.
- 246. Bailes JE: Telemedicine systems: applications in trauma. Trauma Tactics Conference, Orlando, FL., Feb. 1998.
- 247. Bailes JE: Technique and indications for carotid endarterectomy (Session Moderator) Joint Section AANS/CNS and ASITN Stroke Meeting, Orlando, FL., Feb. 1998.

- 248. Bailes JE: Endovascular and surgical therapy for vascular malformations and stroke (Panelist). Joint Section AANS/CNS and ASITN Stroke Meeting, Orlando, FL., Feb. 1998.
- 249. Bailes JE: Chimame “blister” aneurysms. Barrow Neurological Institute Annual Conference, Phoenix, AZ, March 1998.
- 250. Bailes JE: Applications of telemedicine systems in neurosurgery. Barrow Neurological Institute Annual Conference, Phoenix, AZ, March 1998.
- 251. Bailes JE: Strategies for developing a neurosurgical practice partnering with managed care. American Association Neurological Surgery Annual Meeting, Philadelphia, PA, April 1998.
- 252. Bailes JE: Monitoring techniques in carotid endarterectomy. American Association Neurological Surgery Annual Meeting, Philadelphia, PA, April 1998.
- 253. Bailes JE: Sports Injuries: Special considerations for the head and spine. Indiana Spine Trauma Symposium, Indianapolis, IN, May 1998.
- 254. Bailes JE: Athletes: Factors in the decision to allow returns to play. . Indiana Spine Trauma Symposium, Indianapolis, IN, May 1998
- 255. Bailes JE: Applications of telemedicine and the Internet in neurological surgery. American Association Neurological Surgery Annual Meeting, Philadelphia, PA, April 1998.
- 256. Bailes JE: Developing stroke centers – “Brain Attack” in the community setting. American Association Neurological Surgery Annual Meeting, Philadelphia, PA, April 1998.
- 257. Bailes JE: Helmet and equipment design for contact sports. American College Sports Medicine. Orlando, FL., June 1998.
- 258. Elorifai AM, Taylor MJ, Bailes JE, Shih SR et al.: Further development of ultraprofound hypothermia and blood substitution in a canine model with a view to clinical trials. Society of Cryobiology Annual Meeting, Pittsburgh, PA, July 1998.
- 259. Bailes JE: Use of hypothermia and blood substitution for trauma resuscitation. American College of Surgeons, Annual Meeting, Orlando, FL, October 1998.
- 260. Bailes JE: Operative treatment of “giant” intracranial aneurysms. American College of Surgeons, Annual Meeting, Orlando, FL., October 1998.
- 261. Bailes JE: Minor head injuries: incidence, pathophysiology, and treatment. American College of Surgeons, Annual Meeting, Orlando, FL, October 1998.
- 262. Bailes JE: Management of athletic head and spinal injuries. American Association of Neurological Surgeons, Annual Meeting, Seattle, WA, October 1998.
- 263. Bailes JE: Current technologies for surgical practices. American Association of Neurological Surgeons Annual Meeting, Seattle, WA, October 1998.
- 264. Bailes JE: Internet and its applications in medicine and neurosurgery. American Association of Neurological Surgeons Annual Meeting, Seattle, WA, October 1998.

- 265. Bailes JE: Neurosurgical evaluation and treatment of brain and spinal injuries. Medical Management Group of Orlando. Orlando, FL, Jan. 1999.
- 266. Bailes JE: Organization and function of a county-wide emergency medical services system. Orlando, FL, Jan. 1999.
- 267. Bailes JE: Carotid endarterectomy and stenting. Joint meeting of Section of Cerebrovascular Surgery and ASITN. Nashville, TN Feb. 1999.
- 268. Bailes JE: When to play following athletic central nervous system injury. 23rd Annual Internal Medicine Conference, Orlando, FL, Mar. 1999.
- 269. Bailes JE: Issues in management of injured athletes. American Association of Neurological Surgeons Annual Meeting, New Orleans, LA, April 1999.
- 270. Bailes JE: Issues in management of injured athletes. American Association of Neurological Surgeons Annual Meeting, New Orleans, LA, April 1999.
- 271. Bailes JE: Establishing a modern medical practice utilizing networking and high technology. American Association of Neurological Surgeons Annual Meeting, New Orleans, LA, April 1999.
- 272. Bailes JE: Head injuries in athletes. Spinal Symposium on Athletic Injuries. American Association of Neurological Surgeons Annual Meeting, New Orleans, LA, April 1999.
- 273. Bailes JE: Management of athletic head injuries. Sports related nervous system injuries annual meeting, Orlando FL May 1999.
- 274. Bailes JE: Management of spinal injuries in athletes, Sports related nervous system injuries annual meeting, Orlando FL May 1999.
- 275. Bailes JE: Head and spinal injuries in sports. Florida Athletic Trainers Association Annual Meeting. Orlando, FL. June 1999.
- 276. Bailes JE: Surgical treatment of stroke. St. Luke's Hospital Annual Stroke Meeting. Lake Geneva, WI Sept. 1999.
- 277. Bailes JE: Surgical treatment for cerebral aneurysms and AVM's. St. Luke's Hospital Annual Stroke Meeting. Lake Geneva, WI Sept. 1999.
- 278. Bailes JE: Teleradiology and EMS in future treatment of the stroke patient. St. Luke's Hospital Annual Stroke Meeting. Lake Geneva, WI Sept. 1999.
- 279. Bailes JE: Concussion in sports. Congress Neurological Surgeons Annual Meeting. Boston, MA Nov. 1999.
- 280. Bailes JE: The neurosurgeon's role in future EMS systems. Congress of Neurological Surgeons Annual Meeting, Boston, MA, November 1999.
- 281. Bailes JE: Head injuries in sports, Congress of Neurological Surgeons Annual Meeting. Boston, MA, November 1999.
- 282. Bailes, JE: Development and structure of EMS systems for stroke and neurotrauma. Gateway to

the Brain Conference. Orlando Science Center, Orlando, FL, November 1999.

- 283. Bailes JE: Carotid endarterectomy. Indications and results. Joint Meeting ASITN and JSCVS. New Orleans, LA. February 2000.
- 284. Bailes JE: Symposium moderator. Skull base meningiomas. North American Skull Base Society. Phoenix, AZ. February 2000.
- 285. Bailes JE: Concussion management in athletes. American Association Neurological Surgeons Annual Meeting. San Francisco, CA. April 2000.
- 286. Bailes JE: Concussion in athletes-classification systems. American Assoc Neurological Surgeons Annual Meeting. San Francisco, CA. April 2000.
- 287. Bailes JE, Jordan BD: Concussion history and current neurological symptoms among retired professional football players. American Academy of Neurology Annual Meeting. San Diego, CA. May 2000.
- 288. Bailes JE: Management of concussion in athletes. Neurosciences Teaching Weekend. Morgantown, West Virginia. September 2000.
- 289. Bailes JE: Surgical treatment of stroke. Neurosciences Teaching Weekend. Morgantown, West Virginia. September 2000.
- 290. Bailes JE: Surgical treatment of stroke. Hal Wanger Family Medicine Conference. Morgantown, West Virginia. October 2000.
- 291. Sadrolhefazi A, Miele V, Carr A, Bailes JE: A Retrospective Review of Neurological Injuries Related to Sports and Recreational Activities. American Association Neurological Surgeons Annual Meeting Toronto 2001.
- 292. Sadrolhefazi A, Miele V, Carr A, Bailes JE: A Retrospective Review of Neurological Injuries Related to Sports and Recreational Activities. The Neurological Society of the Virginias Annual Meeting, Homestead, VA, January 2001.
- 293. Bailes JE: Intrathecal thrombolysis for aneurismal intraventricular hemorrhage. The Neurological Society of the Virginias Annual Meeting, Homestead, VA, January 2001.
- 294. Carr A, Miele V, Bailes JE: Neurologic Hunting Injuries. Neurotrauma and Sports Medicine for the New Millennium Conference, Park City, UT. March 2001.
- 295. Bailes JE: Spinal stenosis in the athlete. American Association of Neurological Surgeons Annual Meeting. Toronto, April 2001.
- 296. Bailes JE: Skullbase approaches for aneurysms of the vertebrobasilar circulation. Duke University, International Neurosciences Symposium, Raleigh, NC. April 2001.
- 297. Miele V, Sadrolhefazi A, Carr A, Bailes JE: A Retrospective Review of Neurological Injuries Related to Sports and Recreational Activities. Edgar F. Heiskell Memorial Trauma Conference, Morgantown WV. September 2001.
- 298. Carr A, Miele V, Bailes JE, et al: Factors that Influence Neurologic Injuries and Death in ATV Accidents: a Ten Year Retrospective Review at the Jon Michael Moore Trauma Center. Edgar F.

Heiskell Memorial Trauma Conference, Morgantown WV. September 2001.

299. Bailes JE, Miele V, Voelker J: Boxing and the neurosurgeon. Congress of Neurological Surgeons, San Diego, CA. September 2001.
300. Sadrolhefazi A, Miele V, Bailes JE: Influence of Head Position on the Effectiveness of Twist Drill Craniostomy for Chronic Subdural Hematoma. Congress of Neurological Surgeons, San Diego, CA. September 2001.
301. Bailes J, Day A, Miele V: Normal Perfusion Pressure Breakthrough in Small Arteriovenous Malformations. Congress of Neurological Surgeons, San Diego, CA. September 2001.
302. Bailes JE: Emerging surgical indications for stroke. Neurosciences Teaching Weekend, Morgantown, WV. September 2001.
303. Bailes JE: Prehospital care and secondary injury. Presentation for head trauma. Ohio Valley Trauma Update, Wheeling, WV. October 2001.
304. Bailes JE: Intrathecal Thrombolysis for Aneurysmal Intraventricular Hemorrhage. American Academy of Neurological Surgery Annual Meeting. Palm Beach, FL. November 2001.
305. Bailes JE: The medical database for effects of chronic head injury in NFL athletes. Center for the Study of Retired Athletes. Chapel Hill, NC. November 2001.
306. Bailes JE: Management of difficult cerebral aneurysms. Allegheny General Hospital, Pittsburgh, PA. December 2001.
307. Bailes JE: Neurosurgery. Preston Memorial Hospital, Kingwood, WV. December 2001.
308. Bailes JE, Carson LV, Rosen CL: Neurosurgery, Doctors On Call program, broadcast by WVPTV. December 2001.
309. Bailes JE, Miele VJ, Unkelbach MH, Medary M, Voelker JL: Improved outcomes in poor-grade aneurysm patients. Neurological Society of the Virginias meeting, The Homestead, VA, January 2002.
310. Sadrolhefazi A, Miele V, Bailes JE: Influence of Head Position on the Effectiveness of Twist Drill Craniostomy for Chronic Subdural Hematoma. Neurological Society of the Virginias meeting, The Homestead, VA, January 2002.
311. Wilkinson C, Miele V, Nestor S, Rosen C, Bailes JE: Phenytoin and Magnesium Sulfate as Neuroprotective Agents in Acute Spinal Cord Injury. Neurological Society of the Virginias meeting, The Homestead, VA, January 2002.
312. Carr A, Miele V, Bailes JE, Mucha P, Helmkamp J: Factors that Influence Neurologic Injuries and Death in ATV Accidents. Neurological Society of the Virginias meeting, The Homestead, VA, January 2002.
313. Miele V, Hall L, Unkelbach M, Sadrolhefazi A, Carr A, Bailes JE: Soccer Related Neurological Injuries. Neurological Society of the Virginias meeting, The Homestead, VA, January 2002.
314. Bailes JE: Surgical Treatment of Strokes. Fairmont General Hospital, Fairmont, WV. February 2002.

- 315. Bailes JE: Boxing and the neurosurgeon. Neurotrauma and Sports Medicine Review, Orlando, FL. February 2002.
- 316. Bailes JE: Adult spine and spinal cord injuries: return to play issues. Neurotrauma and Sports Medicine Review, Orlando, FL. February 2002.
- 317. Bailes JE: Overview of Neurosurgery. 1st & 2nd year Medical Students February 2002.
- 318. Bailes JE: Head Injuries and Return to Play Issues. Graduate level Athletic Trainers class, West Virginia University, Morgantown, WV. March 2002.
- 319. Bailes JE, Miele VJ, Unkelbach MH, Medary M, Voelker JL: Improved outcomes in poor-grade aneurysm patients. Poster presentation, AANS Annual Meeting, Chicago, IL, April 2002.
- 320. Miele VJ, Price K, Pryputniewicz D, Becker D, Bailes JE: Analysis of Knockouts and Fatalities in the Sport of Professional Boxing. Poster presentation, AANS Annual Meeting, Chicago, IL, April 2002.
- 321. Miele V, Hall L, Unkelbach M, Sadrolhefazi A, Carr A, Bailes JE: Soccer Related Neurological Injuries. AANS Annual Meeting, Chicago, IL, April 2002.
- 322. Carr A, Miele V, Bailes JE, Mucha P, Helmkamp J: Factors that Influence Neurologic Injuries and Death in ATV Accidents. AANS Annual Meeting, Chicago, IL, April 2002.
- 323. Bailes JE, Guskiewicz K, Marshall S: Recurrent Sports-Related Concussion Linked to Clinical Depression. AANS Annual Meeting, Chicago, IL, April 2002.
- 324. Wilkinson C, Miele V, Nestor S, Rosen C, Bailes JE: Phenytoin and Magnesium Sulfate as Neuroprotective Agents in Acute Spinal Cord Injury. AANS Annual Meeting, Chicago, IL, April 2002.
- 325. Bailes JE: What is a Gamma Knife? WVUH Leadership Forum (Managers & Supervisors) Morgantown, WV. April 2002.
- 326. Bailes JE: Vasospasm. ICU In-service, Morgantown, WV. April 2002.
- 327. Bailes JE: Skull Base Approaches to Basilar Aneurysms. International Skull Base Symposium, West Palm Beach, FL. May 2002.
- 328. Bailes JE: Microvascular doppler monitoring during cerebral aneurysms. American Society of Neurophysiological Monitoring Annual Conference, Orlando, FL. May 2002.
- 329. Bailes JE: Stroke. MS 1 class, WVU School of Medicine, Morgantown, WV. May 2002.
- 330. Bailes JE: Neurological consequences of a professional football career. NFL Retired Players' Convention, Phoenix, AZ. May 2002.
- 331. Bailes JE: Vascular concerns. Surgery Clerkship lecture, WVU School of Medicine, Morgantown, WV. June 2002.
- 332. Bailes JE: Neurosurgical Management of the Athlete: the Spectrum of Traumatic Brain Injury in Athletes. New Developments in Sports-Related Concussion, UPMC Conference, Pittsburgh, PA.

July 2002.

- 333. Bailes JE: Tactical Medicine. WV State Police, Charleston, WV. July 2002.
- 334. Bailes JE: Heat Stroke & Dietary Supplements. Aequanimitas Society meeting, Cleveland, OH. August 2002.
- 335. Bailes JE: Tactical Medicine. WV National Guard, Kingwood, WV. August 2002.
- 336. Bailes JE: Management of Head & Neck Injuries in Athletes. ACOS Meeting, Orlando, FL. Sept. 2002.
- 337. Bailes JE: Management of Difficult Cerebral Aneurysms. ACOS Meeting, Orlando, FL. Sept. 2002.
- 338. Bailes JE: CNS Meeting, Philadelphia, PA Sept. 2002.
- 339. Bailes JE: The Role of Gamma Knife in the Neurosurgeon's Armamentarium. Gamma Knife Open House, Morgantown, WV. November 2002.
- 340. Bailes JE: Medical Perspectives on Bioterrorism. Dept. of Justice. Alexandria, VA. December 2002.
- 341. Bailes JE: Concussion. Neurotrauma and Sports Medicine Conference. Orlando, FL. February 2003.
- 342. Bailes JE, Miele V: Fatalities in Organized Sports: What Have We Learned? AANS Meeting, San Diego, CA. April/May 2003.
- 343. Miele V, Price K, Pryputniewicz D, Becker D, Bailes JE: Analysis of Knockouts and Fatalities in the Sport of Professional Boxing. AANS Meeting, San Diego, CA. April/May 2003.
- 344. Bailes JE: Recurrent Sport-Related Concussion Linked to Clinical Depression. AANS Meeting, San Diego, CA. May 2003.
- 345. Bailes JE: Challenges in Identifying & Treating Sports Injuries. AANS Meeting, San Diego, CA. May 2003.
- 346. Bailes JE: Concussions in the NFL. K. Douglas Bowers Orthopedic Lectureship, Morgantown, WV. September 2003.
- 347. Bailes JE: Gamma Knife: Radiosurgery in the Treatment of Brain Tumors. Fall Cancer Conference, Morgantown, WV. October 2003.
- 348. Bailes JE: Telemedicine. International and Virtual Neurological Surgery Colloquium, CNS Meeting, Denver, CO. October 2003.
- 349. Bailes JE: The Science of Sports Medicine. CNS Meeting, Denver, CO. October 2003.
- 350. Miele V, Bailes JE: Neurological Injuries to Occupants riding in the Cargo Area of Pickup Trucks in West Virginia. CNS Meeting, Denver, CO. October 2003.
- 351. Miele V, Becker D, Bailes JE: Death in the Ring – Analysis of 10 Boxing Fatalities. CNS Meeting,

Denver, CO. October 2003.

- 352. Miele V, Carson L, Bailes JE: Acute Subdural Hematoma in a Female Boxer: Case report and a Discussion of Unique Risks to the Female Participant. CNS Meeting, Denver, CO. October 2003.
- 353. Bailes JE: Surgical Treatment of Difficult and Complex Aneurysms. 3rd Annual Temporal Bone Dissection Course and International Symposium on Clinical Neurosciences and Cerebrovascular Skull Base Surgery. Morgantown, WV. October 2003.
- 354. Bailes JE: Sideline evaluation and treatment of closed head injury. Family Practice and Sports Medicine Conference. Huntington, WV. November 2003.
- 355. Bailes JE: Neurosurgical perspective on acute ischemic stroke. AANS Cerebrovascular Section Meeting. San Diego, CA. February 2004.
- 356. Bailes JE: Periprocedural neuroprotection. AANS Cerebrovascular Section Meeting. San Diego, CA. February 2004.
- 357. Bailes JE: Current tenets in management in athletic head injuries. WV Trauma Symposium. Canaan Valley, WV. February 2004.
- 358. Bailes JE: Neurosurgical sports injuries. Synthes Maxillofacial Annual Meeting. Snowbird, UT. March 2004.
- 359. Bailes JE: Contemporary management in neurological sports medicine. J Jay Keegan Memorial Lectureship, University of Nebraska. Omaha, NE. April 2004.
- 360. Bailes JE: Neurosurgical athletic brain injuries. 2004 Sports Concussion and Spine Injury Conference. Boston, MA. May 2004.
- 361. Bailes JE: Temporary paralysis in athletes. Neurosurgical Society of America, Annual Meeting, Santa Fe, NM. June 2004.
- 362. Bailes JE: Boxing/Martial Arts and Concussion. New Developments in Sports-Related Concussion Conference, UPMC, Pittsburgh, PA. July 2004.
- 363. Bailes JE: Head Injury. Emergency/Trauma Symposium 2004, Wheeling, WV. October 2004.
- 364. Bailes JE: CT perfusion studies to define time window for stroke interventions. Neurosurgical Society of the Virginias annual meeting. The Greenbrier, WV. January 2005.
- 365. Bailes JE: Management of severe head injury and intracranial pressure. WV Trauma Symposium, Canaan Valley, WV. February 2005.
- 366. Bailes JE: Management of difficult cervical spine injuries in athletes. Neurotrauma Symposium, Orlando, FL. March 2005.
- 367. Bailes JE: On-field management of the injured athlete. Neurotrauma Symposium, Orlando, FL. March 2005.
- 368. Bailes JE: NATA/AFCA Sparring in football task force recommendations. Sports Related Concussion and Spine Injury Conference, Boston. May 2005.

- 369. Bailes JE: CT perfusion protocol for stroke. Aequanimitas Meeting, Seagrove Beach, FL. June 2005.
- 370. Bailes JE: West Virginia: Electronic medical records. West Virginia Healthcare Summit 2005. The Greenbrier, Lewisburg, WV. August 2005.
- 371. Bailes JE: Electronic health records initiative in West Virginia. Electronic Health Records Initiative Committee, Stonewall Resort, Roanoke, WV. September 2005.
- 372. Bailes JE: Electronic medical records. West Virginia Health Information Management Association annual meeting. Flatwoods, WV. September 2005.
- 373. Bailes JE: Cervical disease. WVUH Spine Conference. Lakeview Resort, Morgantown, WV. October 2005.
- 374. Bailes JE: Steroids in sports. Vital Signs television show, Charleston, WV. November 2005.
- 375. Bailes JE: Giant aneurysms panel discussion. Extracranial and Intracranial Bypass workshop, Barrow Neurological Institute, Phoenix, AZ. February 2006.
- 376. Bailes JE: Concussion and brain injury: treatment with high dose DHA. Management of the Neurotrauma Patient, Toronto, ON. April 2006.
- 377. Bailes JE: Electronic Medical Records. Ohio Valley Medical Center, Wheeling, WV. May 2006.
- 378. Bailes JE: Stroke. State of the Stroke West Virginia meeting, Charleston, WV. September 2006.
- 379. Bailes JE: Head injuries in the elderly. OVMC Trauma Symposium. Wheeling, WV. October 2006.
- 380. Bailes JE: E-Health and the effect on rural America. WV Rural Health Conference, Stonewall Resort, Roanoke, WV. October 2006.
- 381. Bailes JE: Sports injury update. Southern Neurosurgical Society Annual Meeting, Sea Island, GA. March 2007.
- 382. Bailes JE: Importance of HER. National Technology Transfer Center, Wheeling, WV. March 2007.
- 383. Bailes JE: Argument to continue boxing. AANS, Washington, DC. April 2007.
- 384. Bailes JE: Spectrum of outcome of sports concussion. The National Concussion Summit, Marina Del Rey, CA. April 2007.
- 385. Bailes JE: Concussion in sports: state of the science. Moderator, panel discussion. The National Concussion Summit, Marina Del Rey, CA. April 2007.
- 386. Bailes JE: Long Term Cognitive Impairment in the NFL Player. Sports Related Conference on Concussion & Spine Injury, Boston, MA. April 2007.
- 387. Bailes JE, Lovell M: Other studies of retired players. NFL Concussion Summit, Chicago, IL. June 2007.

- Bailes JE, Maroon JC, Casson I: Does concussion lead to pugilistic dementia and alzheimers? NFL Concussion Summit, Chicago, IL. June 2007.
388. Bailes JE: Drug testing, panel discussion. WVU Sports Law Symposium. Morgantown, WV. October 2007.
389. Bailes JE: The neurosurgeon's livelihood in sports medicine. 2007 Annual Clinical Assembly of Osteopathic Specialists. Las Vegas, NV. October 2007.
390. Bailes JE: Is the hassle of setting up and using telemedicine worth the return? 2007 Annual Clinical Assembly of Osteopathic Specialists. Las Vegas, NV. October 2007.
391. Bailes JE: Having long-term results with complex aneurysms: what do I do now? 2007 Annual Clinical Assembly of Osteopathic Specialists. Las Vegas, NV. October 2007.
392. Bailes JE: Tauopathy dementia in the spectrum of athletic brain injury. Neurosurgical Society of the Virginias annual meeting. The Greenbrier, WV. January 2008.
393. Bailes JE: Neurosurgical trauma. NYUSOM Neurosurgery Grand Rounds. New York, NY. March 2008.
394. Bailes JE: NASA, Houston, TX. March 2008.
395. Bailes JE, Roberts L: Doctoring through a media frenzy. AMA Medical Communications Conference, San Diego, CA. April 2008.
396. Bailes JE: Life after sports: the challenges of informed decision making. Sports Concussion Seminar, Marina Del Rey, CA. April 2008.
397. Handley K, Bailes JE: DHA – the important omega 3 fatty acid in brain structure: its relevance in athletic brain injury. Sports Concussion Seminar, Marina Del Rey, CA. April 2008.
398. Bailes JE: Chronic traumatic encephalopathy in the professional athlete. Sports Medicine Conference, Boston, MA. May 2008.
399. Bailes JE, Guskiewicz K, Cantu R, et al: Brain injury panel discussion. Sports Medicine Conference, Boston, MA. May 2008.
400. Bailes JE: Concussion. Athletic Trainers Conference. UGa, Athens, GA. May 2008.
401. Sears B, Bailes JE: Omega 3 fatty acid supplementation reduces the extent of axon damage after brain trauma. ISSAFL 2008, Kansas City, MO. May 2008.
402. Bailes JE: Improving communication during a public health emergency. HLS Conference, Morgantown, WV. June 2008.
403. Bailes JE: Omega 3 EFA and head injury. Zone Labs, Bermuda. July 2008.
404. Bailes JE: Are there long-term neuropathological changes in athletes. New Development in Sports-Related Concussion Conference. Pittsburgh, PA. July 2008.

- 405. Bailes JE, Omalu B: Human and experimental evidence of neurodegeneration in contact sports. American Academy of Neurological Surgeons annual meeting, Phoenix, AZ. September 2008.
- 406. Bailes JE: Is there potential for long-term effects of athletic concussion? Visiting professor, Wayne State University Dept of Neurosurgery. Detroit, MI. October 2008.
- 407. Bailes JE: Use of Omega 3 fatty acids in neural trauma. 2nd International Zone Conference, Anti-inflammatory Medicine. Cancun, Mexico. November 2008.
- 408. Bailes JE: Concussion. American Football Coaches Association annual meeting. Nashville, TN. January 2009.
- 409. Bailes JE: Long-term consequences of athletic mild traumatic brain injury. Interurban Neurosurgical Society annual meeting. Chicago, IL. March 2009.
- 410. Bailes JE: Permanent brain injury – possibly to be caused by contact sports. Grand rounds, University of Illinois Chicago, IL. June 2009.
- 411. Bailes JE: New understanding of causes and consequences of sport-related concussion. Annual meeting Neurosurgical Society of the Virginias, The Greenbrier, WV. January 2010.
- 412. Bailes JE: Concussion 2010 – brain injury and brain armor. Big Sky Athletic Training and Sports Medicine Conference, Big Sky, MT. February 2010.
- 413. Bailes JE: Latest and greatest in traumatic brain injury. WV Trauma Symposium, Roanoke, WV. February 2010.
- 414. Bailes JE: What is chronic traumatic encephalopathy? Cyril H. Wecht Institute of Forensic Science and Law, Concussion Debate, Duquesne University, Pittsburgh, PA. March 2010.
- 415. Bailes JE: Controversies in the management of TBI in professional athletes. AANS, Philadelphia, PA. May 2010.
- 416. Bailes JE: Traumatic brain injury and concussion. Neurological and Neurosurgical Therapeutics 2010: Contemporary Diagnosis and Management. University of South Florida, Tampa, FL. May 2010.
- 417. Bailes JE: Spinal injuries in athletes. WVU Spine Conference, Morgantown, WV. September 2010.
- 418. Bailes JE: Head traumas and concussions. Dieter-Porter Medical Lecture, Washington & Jefferson College, Washington, PA. October 2010.
- 419. Bailes JE: Mining disasters and safety: the Sago Mine experience. Grand Rounds, Allegheny General Hospital, Pittsburgh, PA. December 2010.
- 420. Bailes JE: Reduction of Concussion and Subconcussive Traumatic Brain Injury Through SLOSH Mitigation. Annual meeting Neurosurgical Society of the Virginias, The Greenbrier, WV. January 2011.
- 421. Bailes JE, Maroon JC, Raksin PB: Football injuries and concussion: assessment, return to play, long-term sequelae and the neurosurgeon's role. CNS University of Neurosurgery Trauma Webinar. January 2011.

- 422. Bailes JE: The evolution in our knowledge of concussions: state of the art in 2011. WVATA Annual Sports Medicine Conference, Morgantown, WV. February 2011.
- 423. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? Dept. of Neurosurgery, Stanford University, Stanford, CA. March 2011.
- 424. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? Sally Herrington Goldwater Visiting Professor, Barrow Neurological Institute, Phoenix, AZ. March 2011.
- 425. Bailes JE: Sports-related traumatic brain injury. AANS, Denver, CO. April 2011.
- 426. Bailes JE: Subconcussion impacts: their role in producing long term brain damage. AANS, Denver, CO. April 2011.
- 427. Bailes JE: DHA and the research showing its benefits for the treatment and prevention of head concussions. Collegiate Strength and Conditioning Coaches Association National Conference, Kansas City, MO. May 2011.
- 428. Bailes JE: Subconcussive blows: what are their consequences in sport? Annual National Summit on Sports Concussion, Los Angeles, CA. May 2011.
- 429. Bailes JE: Repeated sub-concussive blows: do they occur and what do we know? National Athletic Trainers Association annual meeting, New Orleans, LA. June 2011.
- 430. Bailes JE: Cumulative brain damage after sports concussion. National Neurotrauma Symposium, Fort Lauderdale, FL. July 2011.
- 431. Bailes JE: Perioperative complications following SAH. University of Miami Aneurysm Workshop. Miami, FL. Nov 2011.
- 432. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? Georgia Neurosurgical Society annual meeting. Atlanta, GA. Dec 2011.
- 433. Bailes JE: Brain protection internally by slosh mitigation. Georgia Neurosurgical Society annual meeting. Atlanta, GA. Dec 2011.
- 434. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? NorthShore University HealthSystem, Medical Grand Rounds. February 6, 2012.
- 435. Bailes JE: Cervical Spine Injuries in Athletes. Dept. of Orthopedics, NorthShore University HealthSystem, Evanston, IL. April 6, 2012.
- 436. Bailes JE: Risks for CTE. Dept. of Neurosurgery, Medical College of Wisconsin. May 18, 2012.
- 437. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? 2012 Annual Clinical Assembly of Osteopathic Surgeons. Chicago, IL. October 1, 2012.
- 438. Bailes JE: Return to Play Issues in Sports-Related Neurotrauma. American College of Surgeons Clinical Congress, Chicago, IL. October 2, 2012.
- 439. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? 6th Annual Fall CME Meeting - Association of Neurosurgery Physician Assistants. Chicago, IL. October 6, 2012.

- 440. Bailes JE: Treating Brain Tumors — A Collaborative Approach to Care. Understanding Cancer Conference, Evanston Hospital, Evanston, IL Dec. 3, 2012.
- 441. Bailes JE: Mild traumatic brain injuries in athletes: are they really mild? The Epilepsy Foundation of Greater Chicago, Evanston, IL February 23, 2013.
- 442. Bailes JE: Concussion in football: An Update. Andrews Institute “Injuries in Football Conference, Destin, FL. March 2, 2013.
- 443. Bailes JE: Concussion management: Best practices for physician diagnosis. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 444. Bailes JE: Concussion management: Role in concussion management. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 445. Bailes JE: Chronic traumatic encephalopathy: Concussion cause vs. concussion correlation. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 446. Bailes JE: Chronic Traumatic encephalopathy: Risks and predispositions. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 447. Bailes JE: Chronic traumatic encephalopathy: Numerator and denominator-population estimates. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 448. Bailes JE: Practice guidelines and impact on concussion. NCAA Concussion Task Force, Indianapolis, IN. April 12, 2013.
- 449. Bailes JE: Mild traumatic brain injuries in athletes: Are they really mild? Keynote address at the American Medical Society for Sports Medicine, San Diego, CA. April 18, 2013.
- 450. Bailes JE: Consequences: Avoidance & managements of concussion & sports Injury. Practical Clinic 037 Concussion & Sports Injury: State of the Art. American Association of Neurological Surgeons Annual Scientific Meeting, New Orleans, LA. April 27, 2013.
- 451. Bailes JE: Historical contributions of neurosurgeons to neurological sports medicine. American Association of Neurological Surgeons Annual Meeting, Saturday, April 30, 2013, New Orleans, LA
- 452. Bailes JE: An Update on premorbid diagnosis of CTE. It's now a reality, but how will it help? 7th Annual National Summit on Sports Concussion, Atlanta, GA. May 10, 2013.
- 453. Bailes JE: Subconcussive blows and risk of CTE. 7th Annual National Summit on Sports Concussion. Atlanta, GA. May 10, 2013.
- 454. Bailes JE: Mild traumatic brain injuries in athletes: Are they really mild? Vivian L. Smith Department of Neurosurgery Grand Rounds, University of Texas Medical School at Houston. October 3, 2013.
- 455. Bailes JE: Concussion – Much ado about nothing? Congress of Neurological Surgery Annual Meeting, San Francisco, CA. October 19, 2013.
- 456. Bailes JE: Frequency, subconcussion: It is real and what is its impact. Congress of Neurological Surgery Annual Meeting, San Francisco, CA. October 21, 2013.

- 457. Bailes JE: Frequency, magnitude, and distribution of head impacts in Pop Warner Football. Congress of Neurological Surgery Annual Meeting, San Francisco, CA. October 21, 2013.
- 458. Bailes JE: Clinical Management of Concussions. New York Neurosurgery at A Cushing Neuroscience Institute Symposium Focus on Brain Tumor, Cerebrovascular and Head Trauma, , New York City, NY. December 14, 2013.
- 459. Bailes JE: Subconcussion and Its Effects. NCAA Safety in College Football Summit, Atlanta, GA. January 22, 2014.
- 460. Bailes JE: Effect of rule changes on mTBI in youth football. NCAA Safety in College Football Summit, Atlanta, GA. January 22, 2014.
- 461. Bailes JE: Long term consequences of repetitive brain trauma: CTE and Neurodegeneration. United Nations Headquarters, New York, NY. January 29, 2014.
- 462. Bailes JE: Concussion in Football: An Update. Andrews Institute "Injuries in Football Conference, Destin, FL. March 8, 2014.
- 463. Bailes JE: The Other Side of the Equation: Concussion Prevention. Andrews Institute "Injuries in Football Conference, Destin, FL. March 8, 2014.
- 464. Bailes JE: UCLA PET Study. NFL Players' Association Mackey-White Committee Meeting, Orlando, FL. March 21, 2014.
- 465. Bailes JE: Overview of new findings on concussion, Practical Course on Neurosurgeons Role in Addressing Concussion and Sports Injury at the 82nd AANS Annual Scientific meeting, San Francisco, CA. April 6, 2014.
- 466. Bailes JE: Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. Discussant at the 82nd AANS Annual Scientific meeting, San Francisco, CA. April 8, 2014.
- 467. Bailes JE: The effects of multiple concussions and subconcussive impacts on brain function. Society Neuropsychology Society Annual Meeting. Dallas, TX. April 26, 2014.
- 468. Bailes JE: Limiting Collisions in High Velocity Sports: Implications for Hit Counts and Monitoring Subconcussive Blows. National Summit on Sports Concussions. Los Angeles, CA. May 2, 2014.
- 469. Bailes JE: "Is My Child's Brain Really Safe in Contact Sports?" 40th Annual Barrow Neurological Institute Neurosurgery Symposium. Phoenix, AZ. May 14, 2014.
- 470. Bailes JE: Agony and Ecstasy: Case Review and Lessons learned. 40th Annual Barrow Neurological Institute Neurosurgery Symposium. Phoenix, AZ. May 14, 2014.
- 471. Bailes JE: Laser Thermal Ablation to Treat Brain Metastases. Oncology Grand Rounds. NorthShore University Health System, Evanston Kellogg Cancer Center. Evanston, IL May 22, 2014.
- 472. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are They Really Mild? Canadian Neurological Sciences Federation 2014 Annual Meeting. Banff, Alberta. June 4, 2014.

473. Bailes JE: Reflections on Neurosurgical Training and Changes in Health Care. The Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY. June 26, 2014.
474. Bailes JE: Agony and Ecstasy: A Neurosurgeon's Role in Defining a New Disease and Treating an Old One. The Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY. June 26, 2014
475. Bailes JE: Overview of Long Term Sequelae. 2014 Sports Concussion Conference, Chicago, IL. July 13, 2014.
476. Bailes JE: Subconcussive Impact and Cumulative Non-Concussive Hits and Their Long-Term Effects on the Brain. 2014 NFHS Concussion Summit, Indianapolis, IN. July 19-21, 2014.
477. Bailes JE: The Association of Boxing Commissions Medical Committee Annual Meeting, Clearwater Beach, FL. July 28, 2014.
478. Bailes JE: Early Experience with Parafascicular Approaches to Brain Tumors. 6 Pillar Approach at Aurora Research Institute, Milwaukee, WI. September 12-13, 2014.
479. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are They Really Mild? Traumatic Brain Injury CME Symposium, University of Louisville, KY. October 10, 2014.
480. Bailes JE: Subconcussion in Impact Sports: Does it Exist and What is the Evidence. 2014 ISAPN Midwest Conference, Naperville, IL. October 10, 2014.
481. Bailes JE: CTE - Is this Real? General Session at the 2014 Congress of Neurological Surgeons Annual Meeting, Boston, MA. October 19, 2014.
482. Bailes JE: Athletic Head Injuries: Return To Play. 2014 Congress of Neurological Surgeons Annual Meeting, Boston, MA. October 20, 2014.
483. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are They Really Mild? 4th Brain & Spine Symposium, Hollywood, FL. October 24, 2014.
484. Bailes JE: Management of Athletic Concussion. 4th Brain & Spine Symposium, Hollywood, FL. October 24, 2014.
485. Bailes JE: Sports Concussion Panel. 2014 Scientific Assembly of the American College of Emergency Physicians, Chicago, IL. October 27, 2014.
486. Bailes JE: Concussion Updates. Northwestern University Department of Athletics Sports Medicine. Evanston, IL. November 3, 2014.
487. Bailes JE: American Brain Tumor Association Presents: The Latest Innovations in Surgically Treating Brain Tumors. American Brain Tumor Association Webinar. November 4, 2014.
488. Bailes JE: Minimally-Invasive Surgical Techniques for Brain Tumor. Advancements in Brain Tumor Diagnosis and Treatments CME Lincolnshire, IL. December 1, 2014.
489. Bailes JE: Scope, Clinical Manifestations, and Overall Impact of Concussive Injury. Concussion Neurosurgery Symposium, University of Chicago, Chicago, IL. December 3, 2014.
490. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are they really mild? NorthShore University

HealthSystem, Department of Medicine - Internal Medicine Symposium, Northbrook, IL.
December 5, 2014.

491. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are they really mild? Staff, Students and Parents of Loyola Academy, Wilmette, IL. January 21, 2015.
492. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are they really mild? American Society of Neuroradiology Annual Meeting, Chicago, IL. April 26, 2015.
493. Bailes JE: Contemporary Management of Sports Concussion: Emerging Themes. American Society of Neuroradiology Annual Meeting, Chicago, IL. April 27, 2015.
494. Bailes JE: Concussion 2015 – Issues and Progress. National Summit on Sports and Concussion Annual Meeting. Los Angeles, CA. June 5, 2015.
495. Bailes JE: Connecting the Dots: Patient advocacy, and serving patients. 2015 American Health Information Management Association Leadership Symposium, Chicago, IL. July 10, 2015.
496. Bailes JE: Early clinical experience with traumatic ICH. Subcortical Surgery Group, Park City, UT. July 31-August 1, 2015.
497. Bailes JE: Hemorrhagic Stroke Overview: The most deadly form of stroke. New England Hemorrhagic Stroke Meeting. Boston, MA. September 22, 2015.
498. Bailes JE: Sulcal and fascicular anatomy (didactic). New England Hemorrhagic Stroke Meeting. Boston, MA. September 22, 2015.
499. Bailes JE: Concussion.....Future directions. The Konkussion Retreat, Toronto, ON. September 25, 2015.
500. Bailes JE: Moderated Panel Discussion: Moving Toward More Targeted Evaluation and Active Management Strategies for Concussion Subtypes. Approach for Treating Concussion Meeting. University of Pittsburgh Medical Center, Pittsburgh, PA. October 14-16, 2015.
501. Bailes JE: Deep Inside the Brain: New tools to treat brain tumors and lesions. The Illinois Society for Advanced Practice Nursing, Naperville, IL. October 16, 2015.
502. Bailes JE: Emerging Strategies in Diagnosis & Management of mTBI. Brain Injury Association of Illinois Conference. Oakbrook, IL. October 23, 2015.
503. Bailes JE: Politics and Sports. University of Massachusetts Lowell, Massachusetts, MA. March 2, 2016.
504. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are they really mild? The Claremont Rehab and Living Center, Buffalo Grove, IL. March 6, 2016.
505. Bailes JE: Concussion Overview. National Sports Concussion Coalition, Chicago, IL. March 23, 2016.
506. Bailes JE: New and Emerging Technologies for Sports Concussion. National Sports Concussion Coalition, Chicago, IL. March 23, 2016.
507. Bailes JE: Mild Traumatic Brain Injury in Athletes: Are they really mild? Grand Rounds Visiting

Professor Lecture at Beaumont Hospital Royal Oak, Detroit, MI. April 1, 2016.

508. Bailes JE: Principles of a Systems Approach for Tumors and Lesions. IU National Resident & Fellow Training Program, Indianapolis, IN. April 16, 2016.

509. Bailes JE: Neurosurgical Care of Athletes - Concussion, Spine, Peripheral Nerve and Return to Play. American Association of Neurological Surgeons Annual Meeting, Chicago, IL. May 1, 2016.

510. Bailes JE: TBI and Concussion conference, Harvard Medical School, Boston, MA. May 20, 2016.

511. Bailes JE: Concussion Overview: What We Know and Future Directions. National Summit on Sports Concussion, Los Angeles, CA. June 10, 2016.

512. Bailes JE: New and Emerging Technologies for Sports Concussion. National Summit on Sports Concussion, Los Angeles, CA. June 10, 2016.

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514. Bailes JE: Emory University, Atlanta, GA. July 1, 2016.

BAILES EXHIBIT 2

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CLINICAL STUDIES

ASSOCIATION BETWEEN RECURRENT CONCUSSION AND LATE-LIFE COGNITIVE IMPAIRMENT IN RETIRED PROFESSIONAL FOOTBALL PLAYERS

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet the chronic neurological effects of recurrent concussion are not well understood. The purpose of our study was to investigate the association between previous head injury and the likelihood of developing mild cognitive impairment (MCI) and Alzheimer's disease in a unique group of retired professional football players with previous head injury exposure.

METHODS: A general health questionnaire was completed by 2552 retired professional football players with an average age of 53.8 (± 13.4) years and an average professional football playing career of 6.6 (± 3.6) years. A second questionnaire focusing on memory and issues related to MCI was then completed by a subset of 758 retired professional football players (≥ 50 yr of age). Results on MCI were then cross-tabulated with results from the original health questionnaire for this subset of older retirees.

RESULTS: Of the former players, 61% sustained at least one concussion during their professional football career, and 24% sustained three or more concussions. Statistical analysis of the data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, $df = 2$, $P = 0.02$) and self-reported significant memory impairments ($\chi^2 = 19.75$, $df = 2$, $P = 0.001$). Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was not an association between recurrent concussion and Alzheimer's disease, we observed an earlier onset of Alzheimer's disease in the retirees than in the general American male population.

CONCLUSION: Our findings suggest that the onset of dementia-related syndromes may be initiated by repetitive cerebral concussions in professional football players.

KEY WORDS: Alzheimer, Concussion, Mild cognitive impairment, Retired professional football players

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Traumatic brain injury (TBI) is an important public health concern, as each year more than 1.2 million Americans suffer head injury (26). More than 50,000 head-related injuries result in a fatality each year in the United States, whereas the overwhelming majority of head injuries are classified as mild traumatic brain injuries that can result in significant cognitive, emotional, and functional disabilities (26). TBI has been identified as a potential risk factor for the occurrence (or early expression) of neurodegenerative dementing disorders, including Alzheimer's dis-

ease (AD) disease and Parkinson's syndrome, and other psychiatric disorders such as clinical depression (8, 13, 21, 25, 28, 31, 35-37, 40). Still, other research findings have not shown this association between TBI and dementia (1, 3, 6, 7, 17, 19, 33, 42). Guo et al. (9) suggested that the severity of head injury is related to the magnitude of AD risk, and that the risk of AD associated with head injury involving loss of consciousness was approximately double that associated with head injury without loss of consciousness. However, they reported that even head injury without loss of conscious-

ness significantly increased the risk of AD relative to no head injury (9).

Mild cognitive impairment (MCI) is a recently established diagnostic classification typically applied to older individuals who exhibit some evidence of cognitive decline (usually in the domain of memory) and perform below expected levels on formal neurocognitive testing, but who have not exhibited a sufficient degree of impairment and/or functional decline to meet diagnostic criteria for dementia (30). MCI is often conceptualized as a transitional state between the cognitive changes of normal aging and dementia, with most recent studies estimating that 10 to 20% of MCI patients convert to a more advanced stage labeled as "dementia" each year, compared with healthy controls who convert at a rate of 1 to 2% per year (5, 22, 39). The majority of patients with MCI who convert to dementia are subsequently diagnosed with probable AD, although a significant percentage is diagnosed with vascular dementia (23). The identification of risk factors for the onset of MCI, and for the conversion of MCI to dementia, is an important step in developing strategies for the prevention and early treatment of these disorders, especially with the emergence of various dementia treatment agents thought to provide the greatest therapeutic yield earliest in the disease process. Although head trauma has been linked to irreversible cognitive deficits (24, 29, 30), its role in causing eventual MCI or AD is less clear. Mayeux et al. (20) reported a 10-fold increase in the risk of developing AD among those individuals who tested positive for the ApoE e4 gene and had a history of TBI, compared with only a two-fold increase in risk with the ApoE e4 gene alone. Other authors have described a genetic vulnerability and redistribution of neurofilaments after TBI resulting from rotational acceleration of the head in the non-athletic population (12, 27).

The relatively high rate of concussive brain injuries in contact sports affords a unique opportunity for exploring both the immediate and long-term consequences of concussion. More than 300,000 sport-related concussions, many of which are recurrent injuries, occur annually in the United States (38). Unfortunately, the long-term effects of these concussions remain largely unclear. Organized sports, however, provides for a unique laboratory for studying the influence of recurrent mild TBI on dementia-related syndromes such as MCI and AD. The sports literature has connected ApoE e4 with chronic TBI in boxers (16), and other studies have shown that the repeated head trauma experienced by boxers can lead to the development of dementia pugilistica—punch drunk syndrome (32). This literature has also carefully defined the neuropathology of dementia pugilistica as involving numerous neurofibrillary tangles in the absence of plaques, in contrast to the profusion of tangles and plaques seen in AD. Lower cognitive performance has also been found in older football players with the ApoE e4 gene, suggesting that there may be an association between these dementia syndromes and either recurrent TBI or recurrent subconcussive contacts to the head (18). The purpose of our study was to investigate the association between previous head injury and the likelihood of

developing MCI and/or AD in a unique group of individuals, namely retired professional football players, who have previous head injury exposure.

PATIENTS AND METHODS

A diverse group of retired professional football players were studied, including recent retirees and those who played professional football before World War II. All participants played a minimum of two seasons of professional football. We studied this group using two self-report questionnaires: a general health survey and a follow-up instrument specifically targeting cognitive decline. It was explained at the beginning of the survey that participants would not be identified and that research records would be kept confidential. By completing and submitting the survey, participants were acknowledging that they agreed to take part in this research study.

General Health Questionnaire

The general health questionnaire was first sent to all living members of the National Football League Retired Player's Association ($n = 3683$) through the Center for the Study of Retired Athletes. The questionnaire asked a variety of questions about musculoskeletal, cardiovascular, and neurological conditions that the retired player experienced during and after his football career. It included questions about the number of concussions sustained during their professional football career (concussion history) and the prevalence of diagnosed medical conditions such as depression, Parkinson's disease, AD, and schizophrenia. Previous concussion was based on the player's retrospective recall of injury events and was defined on the questionnaire as an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating. Additionally, the questionnaire included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being, which addresses how well the retired athlete functions with activities of daily living (41). From the SF-36, we calculated a physical health composite score, which includes scores of physical functioning, role physical, bodily pain, and general health, as well as a mental health component score, which includes scores of vitality, social functioning, role emotional, and mental health. These scores were compared with age- and gender-specific population-based norms established by previous researchers (41).

We initially mailed the general health questionnaire in May 2001, followed by remailings to nonrespondents in August 2001 and February 2002. We then began telephoning nonrespondents at different times of the day and completed the questionnaire over the telephone. We then conducted a reliability check of the general health questionnaire by readministering the instrument to 25 of the original respondents 18 to

24 months later to establish a high level of agreement between selected responses.

Mild Cognitive Impairment Instrument

Approximately 4 months later, a second questionnaire focusing on memory and issues related to MCI was sent to a subset of 1754 retirees. The subset comprised all respondents from the original health questionnaire who were aged 50 years or older. The same instrument was also sent to an informant (spouse or close relative) to collect data on any cognitive problems exhibited by the retiree that were not reported on the retiree's instrument. Results from the MCI questionnaire were then cross-tabulated with results from the original general health questionnaire. MCI was defined according to the following, outlined in the American Academy of Neurology Practice Parameter (30): memory complaint corroborated by a family member; objective memory impairment as determined by neurocognitive testing; intact activities of daily living; and does not meet accepted diagnostic criteria for probable AD or other forms of dementia.

Statistical Analysis

χ^2 tests of association were used to compare proportions in tables; Fisher's exact test was used when 80% of expected cell counts were less than five. Analysis of variance models were used to determine differences among the groups on selected variables. The groups were stratified by concussion history (none, one, two, and three or more). Because of the sample size, some analyses required us to collapse respondents with one and two previous concussions into a single group (one to two previous concussions). We used the Cochran-Armitage trend test to assess linear trends in the proportion of retirees reporting memory impairments and problems across strata of concussion history. Level of significance for all analyses was set a priori at $P < 0.05$. Estimates of the prevalence of AD in the general population of American men, stratified by age, were provided by researchers at the Johns Hopkins University (2).

RESULTS

General Health Questionnaire

Of the original 3683 general health surveys sent to retired players, 2552 (69.3%) were completed. The age of the respondents averaged 53.8 (± 13.4) years, with an average professional football playing career of 6.6 (± 3.6) years. Respondents reported having played organized football (junior high school, high school, college, armed service, and professional) for an average of 15.1 (± 4.3) years. When considering the prevalence of previous concussions, 1513 (60.8%) of the retired players reported having sustained at least one concussion during their professional playing career, and 597 (24%) reported sustaining three or more concussions. Of those retired players who had sustained a concussion during their professional career, more than half reported experiencing loss of consciousness ($n = 817$,

54.0%) or memory loss ($n = 787$, 52.0%) from at least one of their concussive episodes. We asked the retired athletes for their subjective assessment of the long-term consequences of their injuries. Of the retirees who sustained at least one concussion, 266 (17.6%) reported that they perceived the injury to have had a permanent effect on their thinking and memory skills as they have gotten older.

Only 33 (1.3%) retired players reported being diagnosed by a physician as having AD; 15 were undergoing medical treatment for the disease. We observed a higher prevalence of AD in the study population relative to the general American male population (Fig. 1). The overall age-adjusted prevalence ratio for AD was 1.37 (95% confidence interval 0.98–1.56), which indicates that the football retirees have higher prevalence than other American men of the same age. The AD prevalence in the football retirees was particularly increased in the younger age groups (≤ 70 yr), which suggests that this group may have an earlier onset of AD than the general American male population. The average age of the retired players with AD was 71.7 (± 7.62) years (range, 52–83 yr). There was, however, no association between number of concussions sustained as a professional player (none, one, two, and three or more) and a diagnosis of AD (Fisher's exact test, $P = 0.24$).

Mental Component Scale (MCS) scores on the SF-36 were similar between the NFL retirees and population-based normative values for all age groups ($P > 0.05$) (Fig. 2); however, retired players with a history of concussion, especially recurrent concussion, scored lower (worse) on the MCS than those without a history of recurrent concussion ($F [3,2146] = 19.29$, $P = 0.001$). The lowest MCS scores were observed in those with the most reported concussions (Table 1). The group who experienced three or more concussions also scored significantly worse than the normative group on the age-matched MCS (50.31 versus 52.42).

Mild Cognitive Impairment Instrument

Results of the follow-up MCI and memory questionnaires were analyzed based on responses from 758 retired players (average age, 62.4 yr) and 641 retired players' spouses or close relatives. Our findings revealed 22 cases of physician-diagnosed MCI and 77 cases of retirees who have significant

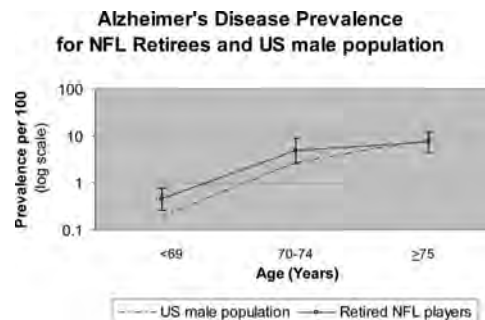


FIGURE 1. Alzheimer's disease prevalence ratios for the American male population and National Football League (NFL) retirees. Error bars indicate 95% confidence intervals.

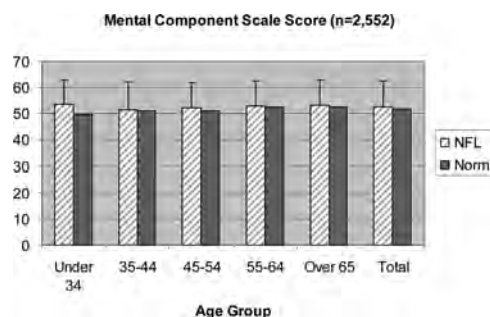


FIGURE 2. MCS scores for the NFL retirees and population norms by age. "Total" is age-standardized; error bars indicate 95% confidence intervals.

TABLE 1. Mental Component Scale score by concussion history in retired National Football League players aged 50 years or older^a

No. of previous concussions	Mean MCS score and 95% CI	Standard deviation
0 (n = 814)	54.35 (53.77, 54.94)	(8.50)
1 (n = 429)	52.63 (51.73, 53.52)	(9.47)
2 (n = 374)	52.97 (52.03, 53.91)	(9.22)
3+ (n = 533)	50.31 (49.35, 51.27)	(11.26)

^a MCS, mental component scale; CI, confidence interval. $P < 0.001$; β -1.51 (0.26).

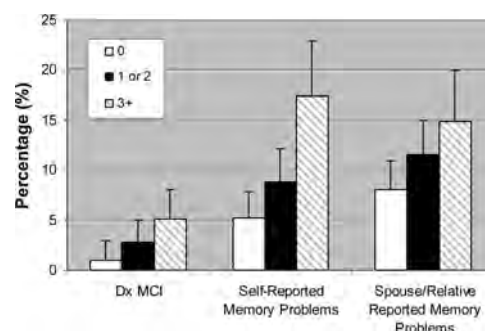


FIGURE 3. Percentage of retired players aged 50 years or older with a diagnosis of MCI and memory problems (self-reported and reported by a spouse or close relative) by concussion history (none, one, two, and three or more). Error bars indicate 95% confidence intervals. $P < 0.007$.

memory impairment as determined by their spouse or close relative. Further analyses of these data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, $df = 2$, $P = 0.02$); self-reported significant memory impairments ($\chi^2 = 19.75$, $df = 2$, $P = 0.001$); and spouse/relative-reported significant memory impairments ($\chi^2 = 6.05$, $df = 2$, $P = 0.04$). Retired players with three or more reported concussions had a fivefold prevalence of being diagnosed with MCI and a threefold prevalence of reported significant memory problems compared with those players without a history of concussion (Fig. 3). There was no association between MCI and other systemic factors such as coronary heart disease, hypertension, diabetes, or osteoarthritis. Although we found an association between diagnosis of MCI and stroke, this association does not detract from the association between MCI and concussion history. Only three (13.6%) of the 22 MCI cases involved stroke, and we do not know which diagnosis came first.

DISCUSSION

These data suggest that a history of concussion, particularly recurrent concussion, may be a risk factor for the expression of late-life memory impairment, MCI, and AD. Although the

clinical samples studied are relatively small, retired professional football players were found to have a progressive decline in mental health functioning and a higher rate of memory problems and cognitive decline associated with a history of concussion. Retired players with a history of three or more concussions were at highest risk of being diagnosed by a physician as having MCI and of having significant memory problems based on their own account and the observations of their spouse or caregiver.

Data from a small sample of retired athletes medically diagnosed with probable AD also suggests a trend toward earlier disease onset and higher disease prevalence in younger cohorts relative to the general population (Fig. 1). Despite the earlier onset of AD, we failed to find an association between previous concussion and lifetime onset of AD. The cumulative effect of sub-concussive and concussive contacts to the head sustained by professional football players may promote an earlier expression of AD; however, the factor of age eventually overwhelms this factor and prevents it from becoming an independent predictor of lifetime onset of AD. Thus, the lines in Figure 1 representing the two groups (American male population and retired NFL players) eventually converge.

The number of individuals in the United States with AD was estimated at 2.32 million in 1997, and it is projected that the prevalence will nearly quadruple in the next 50 years, by which time 1 in 45 Americans will be afflicted with the disease (2). As a result, AD is sure to place a large burden on the country's health care system in the decades ahead. For this reason, identification of factors associated with precursor conditions to AD are of interest. The pathology is characterized by cerebral atrophy most severe in frontal, temporal, and parietal lobes resulting in a dramatic reduction of brain weight (normal, 1500–1800 g; AD, 850–1250 g). Microscopic findings include senile plaques, neurofibrillary tangles, and granulovascular degeneration. Biomechanically, there is a 50 to 90% reduction in choline acetyltransferase (5, 15, 17, 23, 36, 37, 39). Clinically, AD presents with a progressive decline in cortical functions principally affecting memory, language, and executive functioning, followed by increasing neurobehavioral and

neuropsychiatric deficits in more advanced stages of the disease (2, 5, 6).

The study of MCI and AD is challenging because of the difficulties in diagnosing the conditions. Both conditions can be evaluated using several measures, but they cannot be diagnosed solely on neuropsychological assessment. Petersen et al. (29, 30) state that the usefulness of any neuropsychological battery for identifying cases of MCI depends on its composition, size, and supporting data. The battery should include measures of new learning, delayed recall, attention, and executive function. Neuroimaging is also considered a powerful tool for the differential diagnosis of cognitive impairment and tracking change (30). Hippocampal atrophy has been identified in amnesic MCI relative to cognitively intact controls, and it is believed that volumetric measurement of this atrophy can predict the rate of conversion from MCI to AD (15).

The human ApoE gene encodes a cholesterol carrier lipoprotein (apolipoprotein E) that is made in the liver and brain and is important in the transport of lipids in the brain. There are three allelic forms (ApoE e2, e3, e4) that give rise to six possible genotype combinations. ApoE plays an important role in the response of the brain to injury. After accelerator forces are imparted to the brain, there is an accumulation of beta amyloid and tau proteins within hours of injury within the neuronal body (12). Possession of the e2 allele is now believed to be underrepresented in AD and may be protective (22). On the other hand, possession of ApoE e4 increases the risk of AD, shifts onset to an earlier age, increases the accumulation of amyloid beta protein in AD and TBI, and decreases recovery after TBI (6, 7, 12, 19, 20).

The sports literature also suggests that possessing the ApoE e4 allele results in greater cognitive impairment after mild repetitive head injury. Older professional football players with the ApoE e4 allele score lower on cognitive tests than players without the allele or less experienced players of any genotype (18). The study clearly suggests that the cognitive status of athletes with repeated head trauma is influenced by age, inherited factors such as ApoE e4, and cumulative exposure to head contact.

Jordan et al. (16) came to similar conclusions in their study of boxers. The boxers with higher exposure (defined by number of bouts) had significantly higher chronic brain injury scores than those with low exposure. Boxers with low exposure had low chronic brain injury scores irrespective of ApoE e4 allele genotype, whereas those with high exposure and the ApoE e4 allele had higher chronic brain injury scores than boxers with high exposure and no ApoE e4 allele. Possession of the ApoE e4 allele was associated with an increased severity of neurological deficits in the high-exposure boxers.

To our knowledge, our study is unique in evaluating the risk of recurrent mild TBI in the development of later-life memory disorders and MCI. These data describe a significant association between recurrent concussion and MCI, as well as with self-reported memory impairments confirmed by a spouse or close relative. Retired professional football players with three or more concussions were twice as likely to be

diagnosed with MCI as those with one or two previous concussions, and five times more likely than those with no previous concussions. This trend continued with respect to self-reported significant memory problems. These findings suggest that the clinical features of dementia-related syndromes, such as reductions in synaptic density, loss of neurons, and granulovacuolar degeneration, may be initiated by repetitive cerebral concussions. Other recent peer-reviewed studies of recurrent concussion have identified an acute cumulative effect of concussion as measured by increased symptomatology or slowed recovery on symptom checklists and neuropsychological tests after subsequent injuries in high school and collegiate athletes (4, 10, 11, 14). These acute or short-term consequences of recurrent concussion should be of great interest to the sports medicine community, especially given that they parallel our findings of more chronic consequences after years of playing football.

Our study is influenced by the limitations of any retrospective self-report study. The study is limited by the uncertainty of how well the retired players recalled the concussions sustained during their careers and the accuracy of reporting memory problems and diagnosis of MCI. Recent literature has reported selective preservation of older information in subjects with AD-related dementia, which suggests that recollection of events involving previous injuries is not unlikely in these retired athletes (34). The purpose of the spouse or close relative questionnaire was to confirm the retired players' memory status and any physician-diagnosed MCI. For cases in which there was disagreement in the responses of the retiree and the spouse or relative, phone calls and medical records were used to confirm the diagnosis. When the difference in responses could not be reconciled, the case was eliminated from the analyses. Another limitation of our study is that we do not currently know the ApoE allele form of these retired players, which might help to better understand some of these relationships.

CONCLUSIONS

Despite the limitations, these data suggest some very interesting findings—that a history of recurrent concussions, and probably sub-concussive contacts to the head, may be risk factors for the expression of late-life memory impairment, MCI, and AD. Our findings demonstrate a dose-response relationship between concussion and an increased lifetime burden; however, prospective longitudinal cohort studies are necessary to determine causality. Future prospective studies should implement genetic testing, more rigorous diagnostic criteria, historical documentation, and extensive serial evaluations (e.g., neuropsychological testing, functional neuroimaging) to clarify the direct or mitigating effects of concussion on lifetime risk of dementia or other neurological disorders.

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Acknowledgments

We thank Ron Brookmeyer, Ph.D., of the Johns Hopkins University, for providing data on the projected prevalence of Alzheimer's disease in the general American population.

COMMENTS

The significance of repeated concussions is a question of great interest to all athletes, from players in grade schools to professionals. Anecdotes suggest that repetitive concussions may have a detrimental effect, but more rigorous analyses of this question have been less conclusive. In this report, Dr. Guskiewicz et al. surveyed retired professional football players, first by asking them to complete a general health questionnaire and subsequently by sending them a second questionnaire focusing on memory problems and cognitive impairment. Their data suggest that recurrent concussions seem to be related to mild cognitive impairment diagnosed by a physician and to be related to self-reported memory problems. These associations seemed to be stronger in patients with three or more reported concussions. Alzheimer's disease may have occurred at an earlier age in former National Football League players than in the population as a whole, but the number of patients with this diagnosis was quite small.

Like all retrospective studies that rely upon self-reported medical histories and health problems, this one is subject to bias in the accuracy with which problems were recalled and reported. Nevertheless, these results are of considerable interest. The authors make appropriate recommendations for further prospective studies to include such factors as genetic testing, standardized diagnostic criteria, and more extensive evaluation of players with concussion, perhaps including neuropsychological testing and functional neuroimaging.

Alex B. Valadka
Houston, Texas

The safety of contact sports and likelihood of neurologic impairment occurring after retiring from the sport are of obvious concern to athletes and to parents deciding on which sports they should allow their kids to participate in. Studies such as this have the potential to provide important information in this regard. Unfortunately, this particular study is confounded by a critical design flaw of relying on retired athletes to accurately recall events from decades earlier and relating those events to their current memory problems. The study would have been much stronger had the authors corroborated the frequency and severity of concussions sustained with independent sources.

Donald Marion
Boston, Massachusetts

Thank you for the opportunity to comment on this excellent and extremely important study. The authors have used the tremendous resource of a database of the National Football League Retired Players Association, which contains 3683 individuals who played football at a high level for an average of 15 years (minimum six yrs of professional-level football). Using carefully constructed retrospective questionnaires, they have shown a strong association between three or more concussions sustained during a players' professional football career and mild cognitive impairment.

Although this evidence was the most compelling, they also showed an earlier onset and increased incidence of Alzheimer's disease in this group of professional football players who received concussions frequently than in the general age-matched male population in the United States.

This study has important and far-reaching implications. To my knowledge, this is one of few studies to show a positive association between repetitive concussion and long-term cognitive impairment and Alzheimer's disease (1-4). Therefore, this study documents the

dangers of contact sports, such as professional football. As professional football evolves, the speed of the plays appears to be increasing, the prowess, strength, and size of the athletes is measurably increasing, and, therefore, the potential for concussions, especially higher-impact energy concussions, is increasing. It is important to know whether the incidence of multiple concussions per player each year is increasing over time, and this invaluable cohort provides such details by including players with a history as far back as pre-World War II.

What are the implications for the future of the game? Possibly, rules could be tightened to limit the types of dangerous plays, but, in the "heat of the game," this may be unlikely. Helmet design has evolved tremendously in recent years (3), and clearly, studies with kinematic accelerometers of the type used in crash-test dummies by the auto industry should be performed and correlated with the "action replays," which are such an exciting facet of modern televised football. In this way, it may be possible to modify the game in ways that are compatible with increased safety without decreasing the spectator appeal of the game. New types of energy-absorbing foam and plastic are becoming available for football helmets.

However, as with professional boxing, athletes who undertake high-impact sports need to be fully and demonstrably informed of the risks that they undertake in pursuit of their vocation. This important study will provide a basis upon which players' associations and teams can formulate decisions.

Do the implications of these data go further? Many have called for apolipoprotein E genotyping of professional boxers to reduce the risk of precipitating Alzheimer's disease in apolipoprotein E ε4 homozygous boxers. Should the same apply to professional football players, ice hockey players, and rugby players?

The authors have demonstrated that they have access to an enormous "data mine" to test the role of long-term physical fitness upon the development of delayed degenerative joint disease, low back disorders, and cardiovascular mortality. Do the cumulative effects of strains, sprains, and fractures, which are the inevitable consequence of professional football, outweigh the beneficial effect of many years of peak physical fitness upon the musculoskeletal system?

M.R. Ross Bullock
Richmond, Virginia

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Dr. Guskiewicz et al. have assessed by questionnaire a large number of retired professional football players to assess the incidence of concussions and more serious head injuries sustained during their playing careers and to determine whether such injuries influenced the subsequent development of Alzheimer's disease or mild cognitive impairment. Their results indicated that football players with repetitive concussion injuries (three or more) have a fivefold prevalence of mild cognitive impairment and a threefold increase in self-reported

GUSKIEWICZ ET AL.

memory problems. The authors also suggest a 'soft' association between concussion and Alzheimer's disease.

This is an interesting paper that poses an intriguing hypothesis regarding the consequences of recurrent concussion, not only to create short-term problems, but also to accelerate the decline of cognitive function in later years. While tantalizing, the findings are soft. This data is derived from a questionnaire administered to a group that may have substantial bias, especially considering the recent reports and concerns expressed by physicians and the media. How did the authors pare down the original 2552 respondents to 758 whose memory questionnaires were analyzed? Figure one suggests an earlier onset of Alzheimer's disease in respondents aged less than 69 years, but the trend corrects by the age of 75. If the hypothesis is correct, why shouldn't this early separation persist or widen over time?

As usual, the data in sports medicine is difficult to control. Despite its shortcomings, it is reasonable that this paper should be published, not on the basis of its science, but on its conjecture and the need for neurosurgeons to be more aware of the current information in this area.

Arthur L. Day
Boston, Massachusetts

This latest manuscript on the relationship between cognitive impairment and recurrent concussion focuses on players from the National Football League. As in previous studies, there is an association between the frequency of recurrent concussion, the development of mild cognitive impairment, and the suggestion that Alzheimer's disease develops earlier in such patients. This trend is potentially of interest, but a larger sample is necessary.

One concern with the manuscript is the lack of controls in other sports where aggressive behavior is common but concussion is relatively rare, such as in wrestling. There may be genetic linkage to aggressive behavior and cognitive impairment later in life, which is separate from concussion. Perhaps the link is unlikely, but such controls in future studies would help support the hypothesis. Clearly, this is an area of continuing interest and the authors work is important.

Lawrence F. Marshall
San Diego, California

Unfortunately, this manuscript reflects the low priority our society places on the prevention of head injuries and the major sequelae. It attempts to address the significant concern that repeated head injury leads to brain damage. Injury prevention programs, such as ThinkFirst, confront the lack of accurate studies on the potential damage of head trauma such as those sustained by both amateur and professional athletes.

The present study does not dispel uncertainties regarding the relationship between repeated concussions and subsequent onset of brain disorders, most importantly Alzheimer's disease. The study suffers from lack of professionally obtained prospective data. The glaring

deficiency of this study is its reliance on questionnaires from patients and relatives that were obtained retrospectively. Society must provide the author with the necessary funds and incentive to do the study correctly based on professionally obtained prospective data. Regrettably, the questions raised by the authors are of great importance to society and remain unanswered.

Charles H. Tator
Toronto, Ontario, Canada

This is an extremely valuable contribution. Most concussion studies focus on the days and weeks following the injury with the implicit assumption that recovery to preinjury levels is the end of the issue. The present paper provides strong suggestion that some residua of a concussion may not become manifest until decades after the injury. The study also provides a strong rationale for future studies focusing on the effects of concussion on cognitive reserves, rather than simply on performance in the immediate aftermath of injury. Moreover, because the present study demonstrates a dose-response relation between concussion and future cognitive disorder, it highlights the importance of reducing lifetime burden of concussion in athletes.

The authors are to be commended for clearly stating the limitations of their retrospective self-report experimental design. However, the 'gold-standard' methodology would require a multi-decade prospective study. While I think the present findings support the need for a prospective inception-cohort study on this question, this should not overshadow the importance of the present findings and the importance of additional follow-up studies exploring the pathophysiological underpinnings of the present findings.

Joseph Bleiberg
*Neuropsychologist
Washington, D.C.*

This is an important paper on the relationship between cerebral concussion and subsequent cognitive impairment in retired professional football players. Its major flaw, as the authors acknowledge, is that the history of previous concussion was based on the players' 'retrospective recall of injury events.' Nonetheless, their data strongly suggests there is a cumulative deleterious effect of repeated concussion on later cognitive function. It further emphasizes the need to enhance protective measures that minimize concussion in contact sports and to carefully follow players by documenting the number and severity of concussive events throughout their careers. Finally, given the increasing data concerning the long-term risk of greater cognitive impairment for concussed individuals carrying the apolipoprotein E e4 allele, genetic screening and counseling of individuals about to embark on a potentially long career of contact sports should be considered.

Daniel F. Kelly
Los Angeles, California



BAILES EXHIBIT 3

Recurrent Concussion and Risk of Depression in Retired Professional Football Players

KEVIN M. GUSKIEWICZ^{1,2}, STEPHEN W. MARSHALL^{2,3}, JULIAN BAILES⁴, MICHAEL MCCREA^{5,6}, HERNDON P. HARDING JR⁷, AMY MATTHEWS¹, JOHNA REGISTER MIHALIK¹, and ROBERT C. CANTU^{8,9}

Departments of ¹Exercise and Sport Science, ²Orthopedics, and ³Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC; ⁴Department of Neurosurgery, West Virginia University School of Medicine, Morgantown, WV; ⁵Neuroscience Center, Waukesha Memorial Hospital, Waukesha, WI; ⁶Department of Neurology, Medical College of Wisconsin, Milwaukee, WI; ⁷Department of Psychiatry, Florida State University College of Medicine, Tallahassee, FL; ⁸Neurosurgery Service, Emerson Hospital, Concord, MA; and ⁹Neurological Sports Injury Center, Brigham and Women's Hospital, Boston, MA

ABSTRACT

GUSKIEWICZ, K. M., S. W. MARSHALL, J. BAILES, M. MCCREA, H. P. HARDING JR, A. MATTHEWS, J. R. MIHALIK, and R. C. CANTU. Recurrent Concussion and Risk of Depression in Retired Professional Football Players. *Med. Sci. Sports Exerc.*, Vol. 39, No. 6, pp. 903–909, 2007. **Purpose:** The purpose of our study was to investigate the association between prior head injury and the likelihood of being diagnosed with clinical depression among retired professional football players with prior head injury exposure. **Methods:** A general health questionnaire, including information about prior injuries, the SF-36 (Short Form 36), and other markers for depression, was completed by 2552 retired professional football players with an average age of 53.8 (\pm 13.4) yr and an average professional football-playing career of 6.6 (\pm 3.6) yr. A second questionnaire focusing on mild cognitive impairment (MCI)-related issues was completed by a subset of 758 retired professional football players (50 yr and older). **Results:** Two hundred sixty-nine (11.1%) of all respondents reported having prior or current diagnosis of clinical depression. There was an association between recurrent concussion and diagnosis of lifetime depression ($\chi^2 = 71.21$, $df = 2$, $P < 0.005$), suggesting that the prevalence increases with increasing concussion history. Compared with retired players with no history of concussion, retired players reporting three or more previous concussions (24.4%) were three times more likely to be diagnosed with depression; those with a history of one or two previous concussions (36.3%) were 1.5 times more likely to be diagnosed with depression. The analyses controlled for age, number of years since retirement, number of years played, physical component score on the SF-36, and diagnosed comorbidities such as osteoarthritis, coronary heart disease, stroke, cancer, and diabetes. **Conclusion:** Our findings suggest a possible link between recurrent sport-related concussion and increased risk of clinical depression. The findings emphasize the importance of understanding potential neurological consequences of recurrent concussion. **Key Words:** CONCUSSION, HEAD INJURY, NEUROLOGIC, DEMENTIA, PSYCHIATRIC, NEUROLOGICAL RISK FACTORS

Traumatic brain injury (TBI) is an important public health concern; the Centers for Disease Control report that each year, more than 1.2 million Americans suffer head injury. Varying degrees of severity exist, with the majority of these injuries classified as mild. Still,

over 50,000 head-related injuries result in fatalities each year, and many others result in mild to severe physical, cognitive, and psychosocial disability. The psychological sequelae are often debilitating and costly (10) and include short-term or acute, and sometimes lifelong, consequences. Depression is the most cited psychological disturbance after TBI, with prevalence rates from 6% in cases of mild traumatic brain injury (31) to 77% in more severe TBI (20) within the first year after injury. Recently, TBI has been identified as a risk factor for chronic depression, as evidenced by a prospective cohort of retired World War II veterans that were assessed for prevalence of depression several decades after the initial injury. After accounting for age, education, and health conditions, an 18.5% lifetime prevalence of depression was observed in veterans who suffered a head injury in their 20s, which was significantly

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higher than the observed 13.4% lifetime prevalence for those without a history of head injury (16).

TBI has also been identified as a potential risk factor for the occurrence (or early expression) of neurodegenerative dementing disorders, including mild cognitive impairment (MCI), Alzheimer disease, and Parkinson syndrome (1,11,13,28,29,36). Although the formal diagnosis of major depression (2) is not common among patients with Alzheimer disease (39), a depressed mood is frequent and can precede the development of Alzheimer disease. Devanand et al. (9) have reported that even a persistently depressed mood increases in parallel with cognitive failure, and that depressed mood alone was associated with increased risk of incident dementia in a study of elderly individuals. However, the presence of depressed mood also increased with increasing cognitive difficulty, suggesting that it was probably an early manifestation of disease (8).

Much of the research studying the long-term consequences of TBI has focused on severe TBI, whereas studies addressing outcomes of recurrent mild TBI on neuropsychiatric disorders have been overlooked. Despite the recent study by Holsinger et al. (16) reporting that the risk of depression was highest for those with severe head injury, researchers have generated inconsistent findings regarding the distinguishing features and factors associated with depression after TBI, especially *mild* TBI.

The high rate of cerebral concussion, or mild TBI, in certain contact sports affords a unique opportunity to examine the immediate and long-term effects of this injury. The purpose of this study was to gain a better understanding of the long-term consequences of recurrent mild TBI in a group of retired professional football players. More specifically, we investigated the relationship between sport-related concussion and prevalence of lifetime clinical depression.

METHODS

A diverse group of retired professional football players were studied, including recent retirees and those who had played professional football before World War II. All participants played for a minimum of two seasons at the professional level. A general health questionnaire was sent to all living members of the National Football League Player's Association–Retired Section ($N = 3683$) through the Center for the Study of Retired Athletes. The questionnaire involved a variety of items about musculoskeletal, cardiovascular, and neurological conditions that each retired player had experienced during and after his football career. The section on neurological conditions, which was the focus of this paper, included questions about the number of concussions sustained as a player (concussion history) and the prevalence of physician diagnosed psychological and medical conditions, including depression, Parkinson disease, Alzheimer disease, and schizophrenia. The questionnaire included the Short Form 36 Measurement Model for Functional Assessment of Health and Well-Being (SF-36),

which assesses health status and estimates how well a retired athlete functions with activities of daily living. From the SF-36, we calculated a physical health composite score (PCS) that includes scores of physical functioning, role physical, bodily pain, and general health, as well as a mental health component score (MCS) that includes scores of vitality, social functioning, role emotional, and mental health.

Approximately 6 months later, a second questionnaire focusing on memory and issues related to MCI was sent to a subset of 1754 retirees. The subset was comprised of all respondents from the original health questionnaire who were ages 50 and older. The same instrument was also sent to an informant (spouse or close relative) to collect collateral data on any cognitive problems exhibited by the retiree but not personally reported on the retiree's instrument. From the MCI questionnaire, we captured data relative to sadness and feelings of depression, which were cross-tabulated with the results from the original general health questionnaire. Before completing both questionnaires, it was explained that participants would not be identified and that research records would be kept confidential. By completing and submitting the survey, participants were acknowledging and consenting that they agreed to take part in this research study, which was approved by the biomedical internal review board at the University of North Carolina at Chapel Hill.

Previous concussion was based on the player's retrospective recall of injury events and was defined on the questionnaire as an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating.

Chi-square analyses were conducted to identify associations and trends between diagnoses of depression and concussion history. The groups were stratified by concussion history (none, 1–2 previous, 3+ previous). Prevalence ratios were calculated using a binary regression model (log link, binary residual). We used the model to control for the following potential confounding factors: age, years since retirement, number of years played (in quartiles), physical component score on the SF-36, and diagnosed comorbidities including osteoarthritis, coronary heart disease, stroke, cancer, and diabetes. Level of significance for all analyses was set *a priori* at $P < 0.05$.

RESULTS

Of the original 3683 general health surveys sent to retired players, 2552 were returned, for a 69.3% response rate. Age of respondents averaged 53.8 (± 13.4) yr, with an average professional football-playing career of 6.6 (± 3.6) yr. Respondents reported having played organized football (junior high, high school, college, armed service, and professional) for an average of 15.1 (± 4.3) yr, with an average of 24.7

(± 13.7) yr since having last played. In response to the questions on concussion history, 1513 (60.7%) of the retired players reported having sustained at least one concussion during their professional playing career, 884 (36.3%; 95% CI: 34.4, 38.2) reported one or two previous concussions, and 595 (24.4%; 95% CI: 22.7, 26.1) reported three or more concussions. Of those retired players who had sustained concussions, more than half reported experiencing loss of consciousness (817; 54.0%; 95% CI: 51.5, 56.5) or memory loss (787; 52.0%; 95% CI: 49.5, 54.5) from at least one of their concussive episodes. We asked players whether they considered their concussive injuries to have impacted their cognitions later in life. Of the retirees who had sustained one or two previous concussions, 102 (11.5%; 95% CI: 9.4, 13.6) reported that the injuries have had a permanent effect on their thinking and memory skills as they had gotten older. The number and prevalence increased to 185 (31.1%; 95% CI: 27.4, 34.8) in those with three or more previous concussions, suggesting a positive association between a higher number of concussions and the perception that those concussions now negatively affect cognitive functioning ($\chi^2 = 226.71$, $df = 4$, $P < 0.001$). Although these data reflect players' perceptions rather than clinical testing, the relatively high proportion who thought their cognition had been affected is of concern.

Analysis of responses to questions regarding clinical depression revealed that 269 (11.1%; 95% CI: 9.9, 12.3) of the 2434 respondents with complete data reported having been diagnosed previously with clinical depression. The group of retirees diagnosed with depression had lower (worse) mental component scores and physical component scores on the SF-36 compared with retirees not diagnosed with clinical depression (Table 1). There was an association between recurrent concussion and diagnosis of depression ($\chi^2 = 71.21$, $df = 2$, $P < 0.005$), with a significant test for linear trend ($\chi^2 = 63.76$, $df = 1$, $P < 0.005$) suggesting that the prevalence increases in a linear fashion with increasing concussion history. Thus, retired players reporting a history of three or more previous concussions were three times more likely (prevalence ratio of 3.06; 95% CI: 2.29, 4.08) to be diagnosed with depression, and those with a history of one or two previous concussions were 1.5 times more likely (prevalence ratio of 1.48; 95% CI: 1.08, 2.02) to have been diagnosed with depression, relative to retirees with no concussion history (Fig. 1).

Because we were concerned this association could be confounded by other factors, we conducted a multivariate

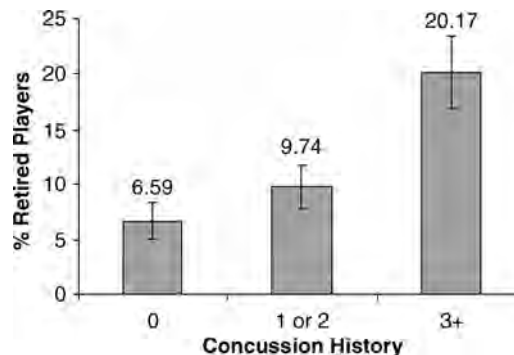


FIGURE 1—Percentage (\pm 95% CI) of retired players with known diagnoses of clinical depression ($N = 269$), stratified by number of previous concussions (none; one or two; or three or more). Test for linear trend: $\chi^2 = 63.76$, $df = 1$, $P < 0.005$.

binary regression analysis in which we controlled for the following factors: age, number of years since retirement, number of years played (in quartiles), physical component score on the SF-36, and diagnosed comorbidities including osteoarthritis, coronary heart disease, stroke, cancer, and diabetes. We observed only a small reduction in the prevalence ratios (2.58; 95% CI: 1.90, 3.55 and 1.39; 95% CI: 1.03, 1.96, respectively) after controlling for these factors, suggesting that the significant association we found between concussion history and diagnosis of depression was not attributable to confounding by these factors.

We were also concerned that the observed association between depression and concussion could be confounded by MCI. Thus, for the subset of subjects who completed the MCI follow-up questionnaire, we conducted additional analyses, controlling for diagnosis of MCI. The prevalence ratios for a history of three or more previous concussions (3.42; 95% CI: 2.12, 5.52) and for one or two previous concussions (1.79; 95% CI: 1.08, 2.94) were essentially unchanged relative to the larger group. Thus, prevalence of MCI did not confound the association between concussion history and diagnosed clinical depression.

Of those reporting any history of depression, 234 (87%; 95% CI: 83.0, 91.0) reported still suffering from the condition, and 124 (46.1%; 95% CI: 40.1, 52.1) were currently being treated with antidepressant medications. Of those 234 retirees with current symptoms of depression, 180 (76.9%; 95% CI: 71.5, 82.3) reported that the condition limits their activities of daily living to some degree. Retired players with depression were more likely to feel as though they should cut down their weekly alcohol consumption compared with those without depression (30.3% compared with 18.0%, respectively) and were more likely to be separated or divorced (14.0% compared with 8.9%, respectively).

In addition to capturing data from the general health questionnaire, follow-up MCI questionnaires were sent to all retired players over the age of 50 yr; 965 of the 1754 surveys were returned, for a 55% response rate (average age = 62.4 yr). We also obtained questionnaires from 797 retired players' spouses or close relatives. Our findings

TABLE 1. Short Form 36 mental component scale score and physical component scale score stratified by diagnosis of clinical depression.

	No Depression Diagnosis ($N = 1999$)	Depression Diagnosis ($N = 254$)	
Mental component scale	54.27 (7.96)	39.28 (12.96)	$F = 673.25$, $df = 1$, 2251; $P < 0.001$
Physical component scale	46.11 (10.31)	42.09 (12.54)	$F = 32.56$, $df = 1$, 2251; $P < 0.001$

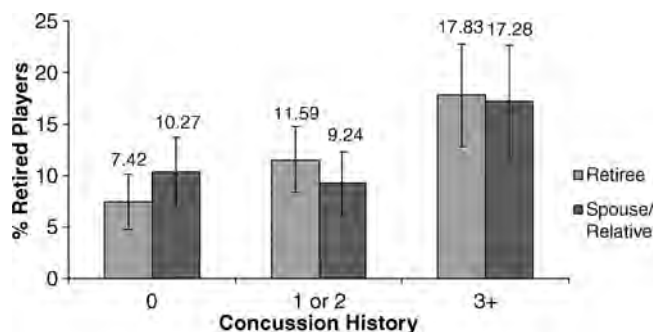


FIGURE 2—Percentage (\pm 95% CI) of retired players and spouses responding that the retiree has “a lot of the time or always” been unusually sad, nervous, or under a lot of stress. Data are stratified by number of previous concussions (none; one or two; or three or more). Test for linear trend: $\chi^2 = 32.96$, $df = 1$, $P < 0.005$.

revealed that a combined 111 (11.5%) of the respondents 50 yr or older reported being unusually sad, nervous, or under a lot of stress “a lot of the time” or “always.” This finding was corroborated with responses by the spouse/close relative (92; 11.5%) when asked the same question, suggesting high consistency (ICC, $R = 0.84$) in the players’ responses to depression diagnosis and their responses to these additional questions regarding sadness, nervousness, and stress. Further analyses of the retired players’ data identified an association between recurrent concussion and the degree to which the retiree responded being “recently unusually sad, nervous or under a lot of stress” ($\chi^2 = 35.39$, $df = 4$, $P < 0.005$), with a significant test for trend ($\chi^2 = 32.96$, $df = 1$, $P < 0.005$) suggesting that the response severity increases in a linear fashion with increasing concussion history (Fig. 2). After controlling for the aforementioned factors, the association remained unchanged.

Finally, in the absence of the retired players’ medical records, we wanted to better understand the validity of self-reported concussions. We asked a sample of 83 retired players to complete the identical general health questionnaire a second time between 36 and 48 months after completing the original questionnaire. Intraclass correlation analysis showed high consistency (ICC, $R = 0.90$) when concussion history questions were compared between the two questionnaires. This led us to believe that the self-reported concussion history was likely accurate.

DISCUSSION

The findings from our study of retired professional football players support the notion that lifetime prevalence of depression and feelings commonly associated with a depressed state increases as a function of previous head injury exposure. Our questionnaire return rate of nearly 70% was unusually high, providing a strong argument to support the validity of the findings. Eleven percent ($N = 269$) of the respondents reported having at least one episode of depression, a finding generally consistent with

the lifetime prevalence in the general U.S. population. Our observed threefold prevalence ratio for retired players with three or more concussions is daunting, given that depression is typically characterized by sadness, loss of interest in activities, decreased energy, and loss of confidence and self-esteem. These findings call into question how effectively retired professional football players with a history of three or more concussions are able to meet the mental and physical demands of life after playing professional football. Furthermore, our findings suggest that a single concussion does not provide the risk for subsequent depression, and they provide an extension to the findings on the cumulative risk of repeat concussion demonstrated in collegiate football players (14). In combination, these studies suggest that football players with three or more concussions are at a threefold risk for sustaining future concussions, with a subsequent threefold risk of being diagnosed with clinical depression compared with those with limited or no prior history.

Depression is common after TBI of all severities (21,33), especially in those involving more severe TBI (1,12,16,20). Our sample included a unique group, retired professional football players, who, for the most part, experienced mild TBI combined with a number of subconcussive impacts, which also may have contributed to an increased likelihood for neurologic decline. In considering our findings, it is important to recognize that individuals suffering from chronic pain are at an increased risk for experiencing depressive states (3,7). This creates a potential confounder when studying professional football players who often experience significant postcareer pain resulting from the many musculoskeletal injuries sustained during their playing days. Because our analysis controlled for these factors, we believe that the identified associations between depression and past concussions are not spurious.

Our findings also suggest that, in general, retired professional football players who have a history of concussion and depressive episodes report greater physical limitations that interfere with their ability to perform daily physical activities compared with those without depression. The SF-36 results for mental and physical functioning reveal that those with a history of depression are more likely to be restricted by muscle and joint pain, feel helpless, have difficulty sleeping, and, in general, feel as though their health is declining. Individuals with a history of depression also reported more alcohol-related problems and were more likely to be separated or divorced.

One of the challenges in studying the association between prior head trauma and depression is that both may be accompanied by cognitive complaints. Furthermore, the cooccurrence of perceived cognitive problems and symptoms of depression has been cited repeatedly in the literature (2,5,30), with one study identifying neuropsychiatric symptoms to be present in 43% of MCI patients within the past month, and depression occurring in 20% of those individuals (23). The perceived cognitive problems reported by patients with depression have been illustrated more

objectively through neuropsychological studies (4,17,40). However, no studies have differentiated between cognitive deficits resulting from mild TBI and depression.

Moreover, researchers have suggested that postconcussion syndrome results from a combination of factors, including biological effects, psychological factors, psychosocial factors (broadly defined), and chronic pain (15,19,24). Many of the specific depressive symptoms are similar to the postconcussion syndrome, making it difficult to distinguish between depression that is secondary to the head trauma and symptomatology consistent with persistent postconcussion syndrome (18). The diagnosis criteria for major depression include the following symptoms: a) diminished ability to think or concentrate, b) indecisiveness, c) fatigue or loss of energy, d) sleep problems, and e) irritability, excessive worry over one's health, and persistent headaches (2). Common lifestyle changes and psychosocial problems, many of which were described by subjects in our study, include strained social relationships, marital and family distress, occupational problems, academic problems, and substance abuse (2).

Despite the challenges of differentiating between these interacting factors, we are confident that our controlled analyses (controlling for MCI and other physical comorbidities) suggest a real association between prior concussions and diagnosis of depression. The next intriguing question becomes, why are prior mild TBI linked to clinical depression?

Explanation for the association between TBI and depression is not fully understood, although several causes have been postulated. These include neurobiological factors such as direct neuroanatomic and neurochemical effects of TBI on mood. Recent studies have found correlations between major depression and structural changes in the brain. Specifically, individuals diagnosed with major depression have smaller hippocampal and amygdala volumes (34,35), structural and morphological changes in the prefrontal and orbitofrontal cortex (22), and basal ganglia structures (6). These structures are all intensively interconnected and are believed to compose a neuroanatomical circuit (26) that plays a key role in mood regulation. The vast majority of head injuries described in our study were mild in nature.

Several psychosocial correlates between TBI and depression have been identified. The most common correlate is the disruption of social relationships. This occurs with family members who bear the burden of long-term care for the TBI patient, and it also occurs among friends and coworkers of the TBI patient (25). Old friendships are often disrupted, and it is often difficult for the TBI patient to form new friendships. Many TBI patients may delay their return to work or never work again, which can negatively influence any relationships with coworkers. The depressed TBI patient most likely does not engage in activities that were once enjoyable; this can cause social isolation and lowered self-image. It is also important to note that any TBI patient with a history of preexisting depression is likely to suffer from bouts of depression after a head injury (12).

Our study is influenced by the limitations of any retrospective self-report study. The study is limited by the uncertainty of how well the retired players recalled the concussions sustained during their careers, and by the accuracy of reporting memory problems and diagnosis of MCI. Recent literature has reported selective preservation of older information in subjects with Alzheimer disease-related dementia, suggesting that recollection of events involving prior injuries is likely in these retired athletes (32). The purpose of the spouse/close-relative questionnaire was to confirm the retired players' memory status and any physician-diagnosed MCI. In cases where there was disagreement in the responses of the retiree and the spouse/relative, phone calls and medical records were used when possible to confirm the diagnosis. When the difference in responses could not be reconciled, the case was eliminated from the analyses. Furthermore, there are several obvious methodological limitations to studying the association between TBI and depression. These limitations include, but are not limited to, the facts that 1) varying diagnostic criteria for TBI, and severity of TBI, exist; 2) cases involving single episodes of depression are often collapsed with cases involving recurrent episodes of depression; and 3) a wide variety of depression-grading scales have been used in the literature. Although much of the literature reports that depressive symptoms are associated with specific subgroups of TBI that are probably linked to injury severity and recovery status at 6 months after injury, there is some indication that cases of mild TBI may result in a higher prevalence of depression. Alexander (1) has revealed that a *mild* TBI group (LOC < 15 min) experienced a significantly higher proportion of cases involving depression than a *severe* TBI group.

CONCLUSIONS

Our findings have implications for understanding the relationship of TBI to lifetime history of depression. TBI can result in diffuse lesions in the brain, depending on the mechanism of injury. These lesions result in biochemical changes, including an increase in excitatory neurotransmitters, which has been implicated in neuronal loss and cell death (38). A potential mechanism for lifelong depression could be this initial loss of neurons, which could be compounded by additional concussions, eventually leading to the structural changes seen with major depression. The structural changes could put the individuals at greater risk of depressive episodes, creating a positive-feedback cycle predicated on the original injury.

Depression can affect one's ability to function in multiple realms, including interpersonal relationships, productivity at work, and self-care. In older adults, depression is associated with significantly higher health care costs (37) and significant risk of functional decline (27). Our findings suggest that professional football players with a history of three or more concussions are at a significantly greater risk for

having depressive episodes later in life compared with those players with no history of concussion. The mechanism of interaction between the pathophysiology of concussion or mild TBI in these players and the lifetime risk of depression is unclear, and it warrants further

investigation. Future prospective studies will be necessary to determine whether there is a causal relationship and whether such structural and biochemical changes take place after multiple concussive episodes in professional football players.

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BAILES EXHIBIT 4

Emerging Histomorphologic Phenotypes of Chronic Traumatic Encephalopathy in American Athletes

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BACKGROUND: We define chronic traumatic encephalopathy (CTE) as a progressive neurodegenerative syndrome caused by single, episodic, or repetitive blunt force impacts to the head and transfer of acceleration-deceleration forces to the brain.

OBJECTIVE: We present emerging histomorphologic phenotypes of CTE that we identified in our cohort of CTE cases with apolipoprotein E genotyping and causes and manners of death.

METHODS: Autopsy brain tissue of 14 professional athletes and 3 high school football players was examined after unexpected deaths. Histochemical and immunohistochemical tissue staining was performed with apolipoprotein E genotyping.

RESULTS: Ten of 14 professional athletes (71%) were positive for CTE: 7 of 8 football players, 2 of 4 wrestlers, and 1 boxer. One of 3 high school players manifested incipient CTE. The age range of those with CTE was 18 to 52 years; they were all male athletes. In all cases of CTE, Alzheimer-type cerebral cortical atrophy was absent; negligible to mild neocortical neuronal dropout was present. The fundamental neuropathologic feature of CTE was the topographic distribution of sparse, moderate, and frequent band-shaped, flame-shaped, small and large globose neurofibrillary tangles and neuritic threads in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, and brainstem nuclei. Sparse to frequent diffuse amyloid plaques may accompany tauopathy and was seen in only 2 CTE cases. No α -synucleinopathy was present. All 7 CTE-positive professional athletes with known apolipoprotein E genotypes had at least 1 E3 allele comprising 5 E3/E3 (71%) and 2 E3/E4 (29%). Alcohol- and drug-related deaths, suicides, and accidental deaths were overrepresented in our CTE cohort.

CONCLUSION: The emerging histomorphologic features of our CTE cohort may specify histologic criteria for CTE diagnosis, may identify emerging histologic variants of CTE and may facilitate more objective surveillance and accurate identification of sentinel CTE cases.

KEY WORDS: American athletes, Chronic traumatic encephalopathy, Histologic subtyping

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In 2002, we identified the first case of cerebral tauopathy in an American football player (AFP), which we termed chronic traumatic encephalopathy (CTE).¹ In 2005 and 2006, we respectively identified the second and third cases of

CTE in AFPs.^{2,3} In 2007, we likewise identified the first documented case of CTE in a professional American wrestler.⁴ Between 2002 and 2009, we examined the brain tissues of a total of 17 deceased professional and amateur athletes (Table 1) and reported the occurrence of parasuicides (the deliberate infliction of injury on oneself or the taking of a drug overdose as an attempt at suicide, which may not be intended to be successful) and suicides in our CTE-positive cases.⁵ In 2009, we also

ABBREVIATIONS: **AFP**, American football player; **ApoE**, apolipoprotein E; **CTE**, chronic traumatic encephalopathy; **MCI**, mild cognitive impairment; **NFT**, neurofibrillary tangle; **NT**, neuritic thread

TABLE 1. Summary of Our Cohort of Chronic Traumatic Encephalopathy Cases^a

Case	Sex/Age, y	Sport	Year	ApoE	Tissue Examined	Cause of Death	Manner of Death
1	M/50	AF	2002	3/3	Whole brain	Coronary atherosclerotic disease, dilated cardiomyopathy, fibrocalcific pericarditis	Natural
2	M/45	AF	2005	3/4	Whole brain	Ethylene glycol poisoning, chemical leptomeningitis, CTE	Suicide
3	M/45	AF	2006	3/3	Autopsy archival brain sections with hippocampus	GSW of the head	Suicide
4	M/24	AF	2007	2/3	Whole brain	Sudden cardiac arrhythmogenic death	Natural
5	M/36	AF	2007	N/A	Autopsy archival brain sections with hippocampus	BFT of the head	Suicide
6	M/40	AW	2007	3/3	Autopsy archival brain sections without hippocampus	Asphyxiation caused by hanging	Suicide
7	M/38	AW	2008	N/A	Autopsy archival brain sections without hippocampus	Acute combined cocaine, diazepam, and methadone toxicity	Accident
8	M/45	AF	2008	N/A	Autopsy archival brain sections with hippocampus	Acute combined cocaine, ethanol, and oxycodone toxicity	Accident
9	M/52	AF	2009	3/3	Whole brain	Acute and chronic pancreatitis, alcoholic steatohepatitis, both caused by chronic alcoholism	Natural
10	M/39	AF	2009	N/A	Autopsy archival brain sections without hippocampus	Acute combined cocaine and heroin toxicity	Accident
11	M/28	MMA	2009	2/4	Autopsy archival brain sections without hippocampus	GSW of the neck	Suicide
12	M/34	AW	2009	3/4	Autopsy archival brain sections with hippocampus	Acute oxycodone toxicity	Accident
13	M/33	AW	2009	3/3	Autopsy archival brain sections without cerebral cortex	Acute combined oxycodone, nordiazepam, carisoprodol, and quetiapine toxicity; dilated cardiomyopathy	Accident
14	M/50	PB	2009	3/3	Whole brain	Positional asphyxiation caused by remote traumatic brain injury	Accident
15	M/18	HSF	2006	N/A	Whole brain	Posttraumatic primary cerebral vasculitis, mild acute bronchial asthma	Accident
16	M/16	HSF	2008	3/3	Whole brain	Craniocerebral injuries	Accident
17	M/17	HSF	2009	3/3	Whole brain	Craniocerebral and cervical spinal injuries	Accident

^aCases 1, 2, 3, and 6 were published previously as sentinel cases.¹⁻⁴ ApoE, apolipoprotein E genotype; AF, American football; N/A, not available (blood was not available for DNA extraction or repeated DNA extraction from formalin-fixed brain tissue failed); BFT, blunt force trauma; MMA, mixed martial arts; GSW, gunshot wound; AW, American wrestling; PB, professional boxing; HSF, high school football.

identified a case of cerebral tauopathy in a retired military personnel with a diagnosis of posttraumatic stress disorder.⁶

We define CTE as a progressive neurodegenerative syndrome caused by single, episodic, or repetitive blunt force impacts to the head and transfer of acceleration-deceleration forces to the brain. CTE presents clinically after a prolonged latent period as a composite syndrome of mood disorders and neuropsychiatric

and cognitive impairment. Direct brain tissue analysis reveals multifocal or diffuse tauopathy, which may be accompanied by low-grade and multifocal white matter rarefaction, microglial activation, and parenchymal histiocytes. Amyloidopathy may be present. CTE usually presents with a prolonged latency period; however, some patients with CTE may not exhibit the classic prolonged latency period before clinical symptoms begin.

Although the underlying mechanism remains poorly defined, the alleles for apolipoprotein E (ApoE) represent important genetic risk factors for adverse outcomes after traumatic brain injury as well as late-onset forms of Alzheimer disease.^{7,8} ApoE is a circulating 34-kDa glycosylated protein, the gene for which is mapped to chromosome 19q. In humans, there are 3 ApoE isoforms, E2, E3, and E4, with 3 corresponding ApoE alleles, E2, E3, and E4. ApoE is primarily synthesized in the liver and is involved in lipid metabolism and cholesterol transport in and out of cells. ApoE is a ligand for low-density lipoprotein receptors and mediates the receptor binding of ApoE-containing lipoproteins to the low-density lipoprotein receptor for cellular uptake and intracellular cholesterol metabolism. In the central nervous system, ApoE is synthesized and secreted primarily by astrocytes and microglia, and its importance is underscored by the absence of most other plasma apolipoproteins in the brain. It is the primary cholesterol transporter in the brain, where it is proposed to function as a ligand directing the delivery of lipids for neuronal repair and remodeling after injury.^{7,9}

We present emerging histomorphologic features of CTE that we are identifying in our emerging CTE cohort with ApoE genotyping, causes, and manners of death. These histomorphologic features may specify histologic criteria for CTE diagnosis, may identify emerging histologic variants of CTE, and may facilitate more objective surveillance and accurate identification of sentinel CTE cases.

Permanent brain damage in boxers (punch drunk syndrome/dementia pugilistica) was recognized in the medical literature in 1928 by Dr. Harrison Martland, a forensic pathologist and Chief Medical Examiner of Essex County, Newark, New Jersey.¹⁰ Seventy-four years later, Dr. Bennet Omalu, another forensic pathologist and medical examiner in Allegheny County, Pittsburgh, Pennsylvania, recognized CTE in football players,^{1-5,11} underscoring the vital role forensic pathologists and autopsies play in the recognition of long-term sequelae of repetitive impacts to the head in sports.⁵ In their literature review in 2009, McKee et al¹² identified a total of 48 neuropathologically verified CTE cases and summarized that CTE is a slowly progressive tauopathy with amyloid plaques (most commonly as diffuse plaques) occurring in less than 50% of cases.

MATERIALS AND METHODS

In each of the 17 cases, the deaths were sudden and unexpected. Full autopsies were performed by forensic pathologists as part of medical examiner/coroner jurisdictional death investigations to determine the cause and manner of death. Autopsy reports were reviewed by the first author (B.O.). Informed consent was obtained from the legal next of kin of each decedent to perform immunohistochemical brain tissue staining if it was not performed as part of the death investigation.

Based on the autopsy protocol of each medical examiner/coroner's office, the whole brain was either fixed in formalin or grossed in the fresh state. When the brain was fixed in formalin, it was grossed by a neuropathologist (B.O.) after a minimum of 2 weeks of fixation in formalin.

When grossed in the fresh state during the autopsy, archival random representative samples of the brain were excised and fixed in formalin by the forensic pathologist who performed the autopsy. These archival sections were later grossed by a neuropathologist (B.O.).

Topographically selected sections of the brain were submitted for a battery of routine and specialized histochemical and immunohistochemical tissue staining protocols including hematoxylin and eosin, Bielschowsky silver impregnation, Luxol fast blue-cresyl violet, polyclonal tau, β -amyloid protein, CD-68, glial fibrillary acidic protein, neurofilament, and α -synuclein immunostaining. The stained brain tissue slides were independently reviewed by 2 neuropathologists (B.O. and R.L.H.) to confirm the presence or absence of cerebral tauopathy and/or amyloidopathy.

The primary neuropathologic criteria for CTE diagnosis included the following: a young active or retired player who played either amateur or professional contact sports and whose postmortem brain tissue revealed the presence of topographically distributed neurofibrillary tangles (NFTs) and neuritic threads (NTs) with or without the presence of diffuse amyloid plaques; the absence of classic or neuritic amyloid plaques; the absence of pathognomonic histomorphology of other types of tauopathies such as progressive supranuclear palsy, corticobasal degeneration, postencephalitic parkinsonism, Guam parkinsonism-dementia; and the absence of Lewy bodies or Lewy neurites.

For ApoE genotyping in the first 3 cases, genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini kit (Qiagen, Valencia, California). Restriction fragment length polymorphism analysis was accomplished by using *HhaI* (New England Biolabs, Beverly, Massachusetts) according to previously published protocols.¹³

For ApoE genotyping in subsequent cases, genomic DNA was extracted from peripheral blood leukocytes or from formalin-fixed brain tissue using the QIAamp DNA Blood Mini kit (Qiagen). The ApoE genotype was ascertained from the amplified DNA by fluorogenic 5' nuclease assays (TaqMan SNP genotyping assays; Applied Biosystems, Foster City, California).

Standard forensic surrogate interviews of surviving next of kin and close family members were performed to identify the presence or absence of terminal premortem profiles and characteristics that may have been common to the decedents whose brains revealed CTE changes. Because of the postmortem retrospective nature of the study, no direct analysis was performed to correlate symptoms and signs, revealed by the surrogate interviews, with pathologic brain tissue changes and findings.

RESULTS

Our CTE cohort comprised a total of 17 athletes (Table 1); all were male, 16 to 52 years old with a mean age of 36 years; there were 8 professional AFPs, 4 professional wrestlers, 1 professional mixed martial arts fighter, 1 professional boxer, and 3 high school AFPs.

CTE was identified in 10 of 14 professional athletes (71%); 7 of the 8 professional AFPs, 2 of the 4 professional wrestlers, and in the only professional boxer in our cohort. The only professional AFP who was negative for CTE in our cohort was 24 years old. Although CTE was identified in the professional boxer in our cohort, it was not identified in the professional mixed martial arts fighter. CTE was also identified in 1 of 3 high school AFPs. All CTE-positive athletes were male, with ages ranging from 18 to 52 years and a mean age of 41 years.

Causes and Manners of Death

The underlying causes of death, contributory factors to death, and manners of death in our 17 cases are listed on Table 1. Suicides and drug-related, natural, and accidental manners of death are overrepresented in our cohort. Three, 5, and 6 of the professional athletes died of natural, suicidal, and accidental causes, respectively. Three of the high school AFPs died as a result of accidental acute traumatic causes sustained while playing football. Case 9, a 52-year-old retired professional football player, died as a result of sequelae of chronic alcoholism. All other accidental causes of death were acute drug toxicities secondary to drug abuse, except 1 case of accidental positional asphyxiation (case 14).

In the CTE-positive professional athletes, there were 2, 4, and 4 natural, suicidal, and accidental manners of death, respectively. One of 2 natural manners of death was secondary to chronic sequelae of chronic alcoholism. Three of 4 accidental deaths were as a result of acute drug toxicities caused by drug abuse.

Pathology

Eight formalin-fixed whole brains (47%) were examined in our cohort. For the remaining 9 cases, archival formalin-fixed autopsy brain tissue sections were examined. The local forensic pathologists who performed the autopsies were less likely to save the whole brains for neuropathologic examination. Of these 9 cases with archival autopsy brain tissues, sections of the cerebral cortex and hippocampus were available in 8 cases and were absent in only 1 case (Case 13), for which only sections of the brainstem and cerebellum were saved without any sections of the cerebral cortex or hippocampus; however, evidence of CTE was not identified in these limited brain sections in this case (Table 2).

None of our CTE cases exhibited diffuse marked cerebral atrophy as one would expect in Alzheimer disease (Figure 1). However, evidence of delayed sequelae of focal traumatic brain injury may be present. In our cohort, sequelae of remote focal traumatic brain injury were seen only in the brain of the professional boxer, who had experienced acute subdural hemorrhage after a past boxing match. The substantia nigra and locus ceruleus were grossly adequately pigmented, mildly to moderately hypopigmented for age in all cases.

From our experience, there are 5 minimalistic primary stains for the diagnosis of CTE: routine hematoxylin and eosin histochemical stain, Bielschowsky's silver impregnation stain, polyclonal tau immunostain, polyclonal β -amyloid stain, and α -synuclein immunostain. Other ancillary stains that may be performed but are not required for a primary diagnosis of CTE include Luxol fast blue-cresyl violet histochemical stain, neurofilament immunostain, glial fibrillary acidic protein immunostain, and CD-68 immunostain.

The fundamental neuropathologic feature of CTE is the presence of sparse, moderate, or frequent band-shaped, flame-shaped, small globose, and large globose NFTs in the brain (Figure 2) accompanied by sparse, moderate, or frequent neuritic

threads (NTs) (Tables 2 and 3). For CTE diagnosis, the quantitative classification of NFT and NT topographic sparse, moderate, and frequent distribution are based on the CERAD plaque density scoring system.¹⁴ Ghost tangles may accompany NFTs and NTs in different regions of the brain.

NFTs and NTs are differentially and topographically distributed in the neocortex, subcortical nuclei/ basal ganglia, hippocampus, brainstem, and cranial nerve nuclei including neurotransmitter synthesizing nuclei: dorsal raphe nucleus, locus ceruleus, basal nucleus of Meynert, substantia nigra (Figure 3).

The cerebral cortex revealed a "skip phenomenon" whereby NFTs and NTs were completely absent in many areas in the cortex and were intermittently present in many areas in the cortex, within the same lobe, in a multifocal randomly situated fashion, located in both the gyri and sulci, without any observable consistent pattern. The skipped areas of the cortex were frequently located adjacent to areas with NFTs and NTs. For the multifocal areas of the cortex with NFTs and NTs, the NFTs and NTs were quantitatively distributed from sparsely to frequently. We did not observe any consistent localization of NFTs and NTs to any specific cortical neuronal laminae. More frequent densities of NFTs and NTs were noted in the depths of sulci and in the perivascular neuropil.

Band-shaped, flame-shaped, and small globose NFTs were found in all regions of the brain, whereas the large globose NFTs were more likely to be found in the subcortical nuclei/basal ganglia and brainstem nuclei. NFTs and NTs were not found in the cerebellum in any of our CTE cases. The temporal cortex and insula cortex may exhibit the largest numbers of NFTs and NTs followed by the frontal cortex and parietal cortex. The occipital cortex exhibited the least numbers of NFTs and NTs and may not show any NFTs and NTs in CTE-positive cases.

Sparse to frequent diffuse cortical amyloid plaques may be present in the neocortex (Figure 4) and were seen in only 2 cases in our cohort (Table 2). The hippocampus may show none to sparse to frequent NFTs and NTs, without any diffuse amyloid plaques (Table 2). Brainstem nuclei may exhibit frequent NFTs and NTs, accompanied by none to sparse NFTs and NTs in the neocortex and basal ganglia (Table 2).

Negligible to mild to moderate neuronal dropout in the neocortex, subcortical nuclei/basal ganglia, and brainstem may be present. Subcortical white matter rarefaction and pallor may be present. Mild diffuse fibrillary astrogliosis of the centrum semiovale, subcortical, and brainstem white matter may be present.

Cerebral amyloid angiopathy, cytomegalic and achromatic neurons, and Lewy bodies and Lewy neurites were absent in all our CTE cases. α -Synuclein glial cytoplasmic inclusions were not identified in any of our cases. Tau immunoreactive astrocytic tufts, astrocytic thorns, and astrocytic plaques were focally present in only 1 case (professional boxer) in very few numbers; these may be seen but are not required for CTE diagnosis.

In the CTE-positive cases, the substantia nigra and locus ceruleus revealed mild to moderate neuronal dropout accompanied by patchy extraneuronal pigment admixed with few

TABLE 2. Distinct Histologic Features of Our Chronic Traumatic Encephalopathy Cases^a

CTE Cases	Histomorphologic Features
Case 1 ^b	Sparse to frequent NFTs; NTs in the cerebral cortex, subcortical nuclei/basal ganglia, and brainstem. No NFTs and NTs in cerebellum. Sparse to frequent diffuse amyloid plaques in cerebral cortex. None to sparse NFTs and NTs in the hippocampus; no diffuse amyloid plaques in the hippocampus
Case 2	Sparse to frequent NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, and brainstem. Moderate to frequent NFTs and NTs in the hippocampus. No NFTs and NTs in cerebellum. No diffuse amyloid plaques in cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or cerebellum
Case 3	Sparse to frequent NFTs and NTs in the cerebral cortex and brainstem. Moderate to frequent NFTs and NTs in the hippocampus. No subcortical nuclei/basal ganglia sections in submitted archival autopsy brain sections. No NFTs and NTs in cerebellum. No diffuse amyloid plaques in cerebral cortex, subcortical nuclei/ basal ganglia, hippocampus, or cerebellum
Case 4	Negative for CTE: no NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or cerebellum. No diffuse amyloid plaques in the brain
Case 5	Sparse to frequent NFTs and NTs in the cerebral cortex, brainstem, and few partial sections of subcortical nuclei/basal ganglia in the submitted archival autopsy brain sections. None to sparse NFTs and NTs in the hippocampus. No NFTs and NTs in cerebellum. No diffuse amyloid plaques in cerebral cortex, hippocampus, or cerebellum
Case 6	Sparse to frequent NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia and brainstem. There were no sections of the hippocampus in the submitted archival autopsy brain sections. No NFTs and NTs in the cerebellum. No diffuse amyloid plaques in cerebral cortex, subcortical nuclei/basal ganglia, or cerebellum
Case 7	Negative for CTE: no NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, or hippocampus. No sections of cerebellum or brainstem in submitted autopsy archival brain sections. No diffuse amyloid plaques in the cerebral cortex, subcortical nuclei/basal ganglia, or hippocampus
Case 8	Sparse to frequent NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, and hippocampus. No sections of the brainstem in submitted autopsy archival brain sections. Sparse to moderate NFTs and NTs in the hippocampus. No NFTs and NTs in the cerebellum. Sparse to frequent diffuse amyloid plaques in the cerebral cortex. No diffuse amyloid plaques in the hippocampus
Case 9	Moderate to frequent NFTs and NTs in brainstem nuclei. None to sparse NFTs and NTs in the cerebral cortex and subcortical nuclei/basal ganglia. Sparse to moderate NFTs and NTs in the hippocampus. No NFTs and NTs in the cerebellum. No diffuse amyloid plaques in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or brainstem
Case 10	None to sparse NFTs and NTs in neocortex and subcortical nuclei/basal ganglia. None to sparse NFTs and NTs in the hippocampus. None to sparse NFTs and NTs in brainstem nuclei. No NFTs and NTs in the cerebellum. No diffuse amyloid plaques in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or brainstem
Case 11	Negative for CTE: no NFTs and NTs in submitted autopsy archival sections of the brain including sections of the cerebral cortex, subcortical nuclei/basal ganglia, and brainstem. No sections of the hippocampus and cerebellum in the submitted autopsy archival sections. No diffuse amyloid plaques in any region of the brain examined
Case 12	Sparse to frequent NFTs and NTs in the cerebral cortex, subcortical nuclei/ basal ganglia, and brainstem nuclei. Sparse to frequent NFTs and NTs in the hippocampus. No NFTs and NTs in the cerebellum. No diffuse amyloid plaques in any region of the brain
Case 13	Negative for CTE: no NFTs and NTs in submitted autopsy archival sections of the brainstem and cerebellum. No sections of cerebral cortex, subcortical nuclei/ basal ganglia, or hippocampus in the submitted autopsy archival brain sections. No diffuse amyloid plaques in sections of the brainstem or cerebellum
Case 14	Moderate to frequent NFTs and NTs in the neocortex, subcortical nuclei/basal ganglia, hippocampus, and brainstem nuclei. No diffuse amyloid plaques in any region of the brain. No NFTs and NTs in the cerebellum
Case 15	None to sparse NFTs and NTs in the neocortex, hippocampus, subcortical nuclei/basal ganglia, and brainstem. No diffuse amyloid plaques in any region of the brain. No NFTs and NTs in the cerebellum
Case 16	Negative for CTE: no NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or cerebellum. No diffuse amyloid plaques in the brain
Case 17	Negative for CTE: no NFTs and NTs in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, or cerebellum. No diffuse amyloid plaques in the brain

^aNFTs, neurofibrillary tangles; NTs, neuritic threads; CTE, chronic traumatic encephalopathy.^bFurther histologic workup of this case after the discovery of the second and third CTE cases revealed more widespread distribution of tauopathy.

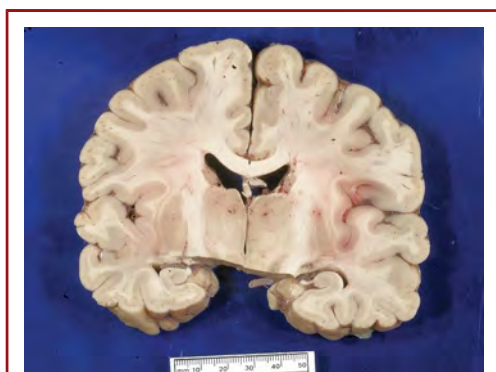


FIGURE 1. Gross photograph of the brain from case 2 that was chronic traumatic encephalopathy positive. The photograph shows a coronal section of the cerebral hemispheres at the level of the thalamus with no cerebral cortical, subcortical, or hippocampal atrophy. This deceased retired National Football League player was 45 years old.

pigment-laden histiocytes. Sparse to frequent NFTs and NTs were also present in the substantia nigra and locus ceruleus.

Other contemporaneous incidental traumatic and non-traumatic brain pathologies exclusive of CTE pathology may be present in the brain of CTE patients, and CTE should be diagnosed independent of these pathologies. However, these contemporaneous pathologies should be identified and reported.

In addition to CTE pathology, acute leptomeningitis and acute axonal injury caused by acute ethylene glycol neurotoxicity was found in case 2 of our cohort. Acute contusions/lacerations of the brain caused by a gunshot wound were found in case 3. Acute cerebral parenchymal contusions caused by blunt force trauma of the head and sparse to marked perivascular and intramural lymphocytic infiltration of many penetrating parenchymal vessels were found in case 5.

Case 6 similarly showed sparse non-necrotizing perivascular lymphocytic infiltration of many penetrating parenchymal vessels

and a pontine capillary telangiectasia. Cases 8, 9, and 12 showed sparse non-necrotizing perivascular lymphocytic infiltration of many penetrating parenchymal vessels. Although case 11 was negative for CTE, chronic non-necrotizing lymphocytic perivascular and intramural infiltration of many penetrating parenchymal blood vessels was found.

In addition to CTE, case 14 showed diffuse right chronic multicystic cerebral traumatic encephalopathy with focal extension to the left cerebral hemisphere accompanied by fenestrations of the septum pellucidum. Nonspecific sparse perivascular histiocytes, some of which were hemosiderin laden, were identified in the Virchow-Robin spaces of penetrating parenchymal blood vessels in all CTE cases. In case 15, a high school football player who died many days after sustaining a mild traumatic brain injury while playing football, amyloid precursor protein immunopositive axonal spheroids and swollen axonal forms as well as marked non-necrotizing posttraumatic cerebral vasculitis were found.

Our cohort included 3 high school AFPs, 16, 17, and 18 years old, who died of complications of traumatic brain and spinal injuries sustained while playing football (Table 1). No NFTs or NTs were identified in the 16 and 17 year olds. However, none to very sparse (1 to several), NFTs and NTs were identified in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, and brainstem of the 18 year old (Table 2). We interpreted this specific observation as an incipient CTE. Although he died of subacute sequelae of traumatic brain injury, he had been playing amateur American football for about 6 years.

We are recognizing 4 distinct emerging histologic phenotypes of CTE in our emerging cohort. The first emerging phenotype is a combination of sparse to frequent NFTs and NTs in the cerebral cortex and brainstem, with or without NFTs and NTs in the subcortical nuclei/basal ganglia, no NFTs and NTs in the cerebellum, and no diffuse amyloid plaques in the cerebral cortex. The second emerging phenotype is a combination of sparse to frequent NFTs and NTs in the cerebral cortex and brainstem with or without NFTs and NTs in the subcortical nuclei/basal

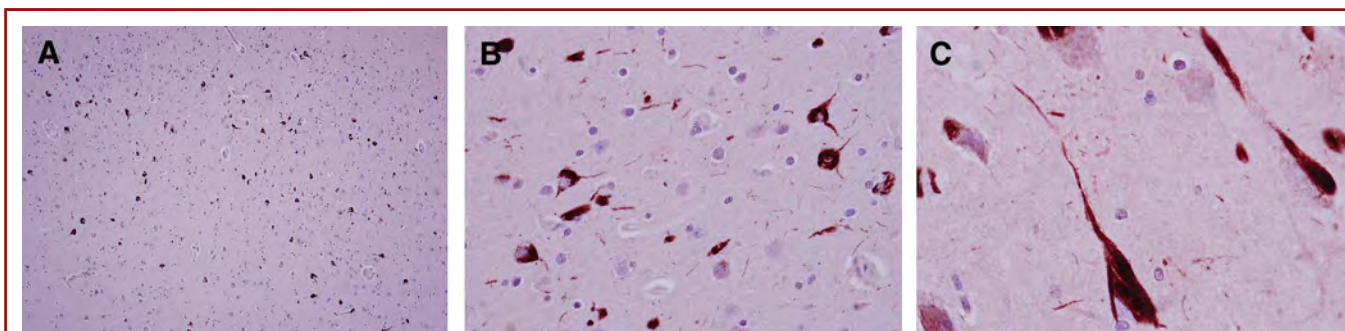


FIGURE 2. Photomicrographs of sections of the brain from case 3 that was chronic traumatic encephalopathy positive. The photomicrographs show tau-immunostained sections of the temporal cortex and subiculum with frequent band-shaped and flame-shaped neurofibrillary tangles and neuritic threads. **A**, temporal cortex, magnification $\times 100$; **B**, temporal cortex, magnification $\times 400$; **C**, subiculum, $\times 600$ magnification.

TABLE 3. Emerging Syndromic Profile Common to Our Chronic Traumatic Encephalopathy–Positive Cases Obtained by Forensic Surrogate Interviews of the Next of Kin and Close Family Members

1. Premortem history of amateur or professional play in organized football, wrestling, boxing, or other high-impact contact sports, short term and long term, months to years, to decades
2. Long latent period between initial play and manifestation of symptoms
3. Progressive deterioration in social and cognitive functioning
a. Loss of memory and memory impairment
b. Loss of language, incoherence
c. Loss of executive functioning
i. Dismal business/investment performance
ii. Dismal money management
iii. Deterioration in socioeconomic status
iv. Bankruptcy
4. Mood and behavioral disorders
a. Paranoid ideations
b. Social phobias
c. Exaggerated responses to life stressors
d. Bouts of anger, worry, and agitation over minor issues
e. Rampant fluctuations in mood (highs and lows; happy and sullen) resembling bipolar disorder
f. Major depression
g. Suicidal ideations and thoughts
h. Parasuicides and suicides
i. Insomnia
j. Hyperactivity, restlessness, high energy and performance drive levels without productive outcomes or results
5. Progressive deterioration in interpersonal and intrafamily relationships
a. Breakdown of intimate and social relationships with spouses, children, other family members, friends, and co-workers
b. Spousal abuse, emotional and physical
c. Spousal separation and divorces
6. Criminal and violent tendencies and behavior
a. Seemingly irrational high risk taking and indulgence in obvious illegal acts
b. Sexual indiscretions and imprudent sexual behavior
7. Abuse of alcohol, prescription, and illicit drugs
8. Increasing religiosity
9. Headaches, generalized body aches, and pain

ganglia, no NFTs and NTs in the cerebellum, and sparse to frequent diffuse amyloid plaques in the cerebral cortex.

The third emerging phenotype is a combination of moderate to frequent NFTs and NTs in brainstem nuclei (brainstem predominant), none to sparse NFTs and NTs in the cerebral cortex and subcortical nuclei/basal ganglia, no NFTs and NTs in the cerebellum, and no diffuse amyloid plaques in the cerebral cortex. The fourth emerging phenotype is a combination of none to sparse (several) NFTs and NTs in the cerebral cortex, brainstem, and subcortical nuclei/basal ganglia (incipient); no NFTs and NTs in the cerebellum; and no diffuse amyloid plaques in the cerebral cortex.

For each emerging phenotype, there may be none to sparse or moderate to frequent NFTs and NTs in the hippocampus, with or without diffuse amyloid plaques in the hippocampus.

ApoE Genotyping

ApoE genotypes were determined in 10 of 14 professional athletes and in 2 of 3 high school football players, giving a total of 12 of 17 cases (71%). Blood samples were not available for 4 professional athletes and 1 high school football player in our cohort, and DNA isolation from archival formalin-fixed brain tissue failed. ApoE genotype was E3/E3 in 6 professional athletes (60%), E3/E4 in 2 professional athletes (20%), E2/E3 in 1 professional athlete (10%), and E2/E4 (10%) in 1 professional athlete. Nine of the professional athletes (90%) with known ApoE genotype had at least 1 E3 allele. Seven of the 10 professional athletes with known ApoE genotype were positive for CTE (70%) and 3 were negative.

All 7 CTE-positive professional athletes (100%) with known ApoE genotypes had at least 1 E3 allele comprising 5 E3/E3 (71%) and 2 E3/E4 (29%). The only professional athlete in our cohort without the E3 allele (E2/E4 genotype) was negative for CTE; the other 2 CTE-negative professional athletes with known ApoE genotypes in our cohort exhibited E2/E3 and E3/E3 genotypes. The professional athlete with an E2/E3 genotype was 24 years old. There were no sections of the cerebral cortex in the submitted autopsy archival brain sections for the professional athlete who was negative for CTE and who had E3/E3 genotype; however, no tauopathy was noted in the submitted archival brainstem sections.

For the 3 deceased high school football players, the ApoE genotype in 1 case could not be determined (blood samples were not available), and the ApoE genotypes in the other 2 were E3/E3 and E3/E3 (Table 1). These 2 cases with known ApoE genotype did not show any histologic evidence of CTE.

Syndromic Profile

Table 3 enumerates the emerging syndromic profile that we observed in our CTE-positive cases, as reported by next of kin and close family members through standard forensic surrogate interviews. These profiles were in part previously published.^{3,5} We could not quantitatively correlate these reported CTE signs and symptoms with CTE brain pathology because of the post-mortem retrospective nature of our study.

DISCUSSION

Based on our experience with our CTE cohort, we recognized 4 emerging and recurring histomorphologic CTE phenotypes described in the Results section. These histologic phenotypes are predicated on the presence or absence of NFTs, NTs, and diffuse amyloid plaques in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, and cerebellum as well as the quantitative topographic distribution and predominance of NFTs, NTs, and

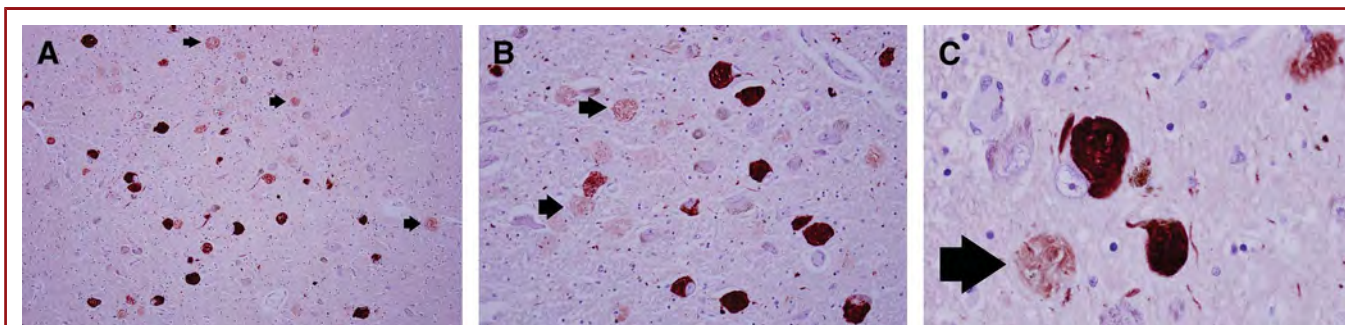


FIGURE 3. Photomicrographs of sections of the brain from case 14 that was chronic traumatic encephalopathy positive. The photomicrographs show tau-immunostained sections of the locus ceruleus with frequent large globose neurofibrillary tangles and neuritic threads. There is marked neuronal loss with frequent ghost tangles representing entombments of dead neurons. The arrowheads indicate ghost tangles. **A**, magnification $\times 100$; **B**, magnification $\times 200$; **C**, magnification $\times 600$.

diffuse amyloid plaques in the cerebral cortex, subcortical nuclei/basal ganglia, hippocampus, and cerebellum.

The hippocampus is frequently spared by tauopathy in CTE cases, whereas tauopathy first appears in the hippocampus in Alzheimer disease.¹⁵ The hippocampus for each CTE case may show none to sparse or moderate to frequent NFTs and NTs with or without diffuse amyloid plaques. We have observed the trend that the hippocampus may not always be available for histologic examination because it was not saved as part of the autopsy archival stock tissues or was destroyed by trauma. The absence of the hippocampus should not preclude tissue analysis and diagnosis of CTE; however, a notation should be made regarding this.

These distinct CTE histomorphologic phenotypes are neither absolute nor rigid classifications; rather they are emerging and recurring histologic phenotypes of CTE that we are observing in our cohort, which may be adapted or modified as we observe more histologic features, if they emerge. These histologic phenotypes may facilitate CTE surveillance and identification and may be used as references or guidelines for accurate tissue CTE diagnosis. Currently, we do not have an explanation for the histologic spectrum of CTE that we have observed thus far, except that CTE may simply be manifesting a phenotypic variation.

For the community-based pathologist and medical examiner, we recommend that only the primary stains, which are enumerated in the Results section, should be used for CTE diagnosis to minimize cost. To further curtail cost, these stains may be performed on a limited number of topographically selected sections of the brain that should minimally include sections of the frontal cortex, temporal cortex, insula cortex, hippocampus, midbrain including the dorsal raphe nucleus, and pons including the locus ceruleus.

Furthermore, caution should be exercised in the diagnosis of CTE in the elderly (older than 65 years of age) to avoid confusing CTE changes with Alzheimer disease pathology, normal age-related changes in the brain, and/or chronic ischemic changes/small vessel disease changes in the brain.⁹ NFTs and NTs, as well as amyloid plaques, may be found in low densities and in a restricted topographic distribution in cognitively normal elderly individuals.¹⁴ The age range of our current CTE positive cohort is 18 to 52 years old.

McKee et al¹² reported 3 cases of CTE in a retired football player and in 2 retired boxers. Their football player was 45 years old and the 2 retired boxers were 73 and 80 years old. Although any conclusions from these 3 cases may be constrained by the

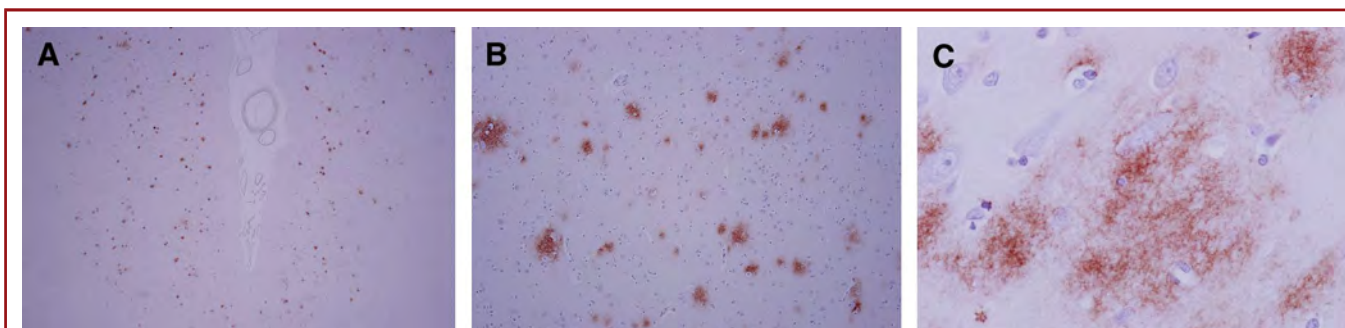


FIGURE 4. Photomicrographs of sections of the brain from case 1 that was chronic traumatic encephalopathy positive. The photomicrographs show β -amyloid-immunostained sections of the frontal cortex with frequent diffuse amyloid plaques. **A**, magnification $\times 20$; **B**, magnification $\times 100$; **C**, magnification $\times 600$.

limited number of cases and the advanced ages of the boxers, McKee et al concluded that the neurofibrillary degeneration of CTE can be distinguished from other tauopathies by preferential involvement of the superficial cortical layers; irregular patchy distribution in the frontal and temporal cortices; propensity for sulcal depths; prominent perivascular, periventricular, and subpial distribution; marked accumulation of tau-immunoreactive astrocytes; and the possible presence of amyloid plaques, most commonly diffuse amyloid plaques.

In our cohort, we did not observe any marked accumulation of tau-immunoreactive astrocytes in any of our cases. Although they are not required for the diagnosis of CTE, we only observed very focal tau-immunoreactive astrocytic tufts, astrocytic thorns, and astrocytic plaques in only 1 case (a professional boxer) in very few numbers. We also observed the skip-phenomenon, described previously, with differential lobar cortical distribution, without any prominent periventricular topographic distribution. Frequent densities of NFTs and NTs were more likely to be found in the depths of the sulci and in the perivascular neuropil. The majority of cases reviewed and reported by McKee et al¹² in their literature review and case report were boxers (39 of 51, 77%), with an age range of 45 to 80 years old, whereas the majority of our cases were football players (11 of 17, 65%) with only 1 boxer, and the age range of our cases was 18 to 52 years old. The differences between their conclusions and ours may suggest that there may be subtle neuropathologic distinctions between CTE found in different sports professionals.

None of our cases exhibited α -synuclein-immunopositive neuronal inclusions (Lewy bodies), glial inclusions, or Lewy threads in the substantia nigra, brainstem nuclei, neocortex, subcortical nuclei, or basal ganglia. As a requisite neuropathologic finding for diagnosis, with the absence of neuronal or glial α -synuclein inclusions in all our cases, it can be deduced that none of our cases manifested the pathology expected in Parkinson disease, diffuse Lewy body disease, or multiple system atrophy. Any parkinsonian motor symptoms that may have occurred in any of our cases may have been attributed to tauopathy, which was present, and not to α -synucleinopathy, which was absent.

We recognize that there are broad spectrums and multifactorial pathoetiologies for cognitive and neuropsychiatric dysfunctions. The histomorphology of CTE, as evinced by our cohort, suggests that cognitive and neuropsychiatric impairment, which may have been observed in our cases, may in part be attributed to impairment of neuronal functioning by tauopathy and by neuronal loss in the frontal, parietal, and temporal lobes; limbic cortex; mesial temporal lobe; and brainstem. The involvement of subcortical and brainstem nuclei by tauopathy and the accompanying neuronal loss in neurotransmitter synthesizing nuclei, as further evinced by ghost tangles (Figure 3), may result in impaired neurotransmitter homeostasis in the brain, which may result in neuropsychiatric impairment and mood disorders. In our CTE cases, the locus ceruleus, dorsal raphe nucleus, and basal nucleus of Meynert were involved and damaged by tauopathy, which would result in impaired synthesis and brain tissue levels

and homeostasis of norepinephrine, serotonin, and acetylcholine, respectively. Impaired neurotransmitter homeostasis in the brain may explain the overrepresentation of suicides and drug-related natural and accidental manners of death in our cohort.

In all CTE-positive cases, NFTs or NTs were not identified in the cerebellum. We currently do not have an explanation for this. We recognize a major shortcoming of our cohort and analysis in that we did not examine whole brains in all cases; however, we also recognize that representative archival autopsy sections of the cerebral cortex, mesial temporal lobe, and brainstem would be sufficient for CTE diagnosis. To circumvent this shortcoming, we recommend that medical examiners and forensic pathologists routinely fix the whole brains of all professional contact sports athletes who undergo autopsy and examine these brains for CTE diagnosis as part of the routine differential diagnoses of causes of death.

We discussed the molecular biology of ApoE in our CTE publications.¹⁻⁴ Friedman et al⁸ reported that the ApoE4 genotype may predict poor functional outcomes in survivors of traumatic brain injury after at least 6 months in 69 survivors of traumatic brain injury. Teasdale et al¹⁶ also reported that patients with ApoE4 are more than twice as likely as those without ApoE4 to have an unfavorable outcome 6 months after head injury. In their cohort of 236 community-dwelling elderly persons, Mayeux et al¹⁷ reported a synergistic 10-fold increase in the risk of Alzheimer disease with both ApoE4 genotype and a history of traumatic head injury. However, they reported that head injury in the absence of an ApoE4 allele did not increase Alzheimer disease risk, and ApoE4 allele alone, without head injury, increased Alzheimer disease risk by only twofold. Millar et al¹⁸ examined a database of 396 patients with traumatic brain injury between 1968 and 1985. They examined their patients at a mean of 18 years after head injury and found that a late decline may occur after head injury; however, there was no clear association with ApoE4 genotype. Kutner et al¹⁹ examined 53 active professional AFPs to determine whether their cognitive status varied as a function of age and ApoE4 genotype. They concluded that older professional football players who possessed the ApoE4 allele scored lower on cognitive tests than did players without this allele or less experienced players of any genotype. Jordan et al²⁰ examined the ApoE genotypes of 24 volunteer and 6 referred boxers aged 23 to 73 years in relation to measures of chronic traumatic brain injury. In their cohort, all boxers with severe impairment by the chronic brain injury scale possessed at least 1 ApoE4 allele. Jordan et al concluded that the possession of an ApoE4 allele may be associated with increased severity of chronic neurologic deficits in high-exposure boxers.

In our cohort, all CTE-positive cases exhibited either E3/E3 or E3/E4 genotypes, with the majority (71%) having the E3/E3 genotype. Overrepresentation of the ApoE3 allele has been reported in patients with tangle-only dementia,^{21,22} whereas the ApoE4 allele has been reported to increase the risk of the development of Alzheimer disease,⁷ with ApoE4/E4 homozygotes having about a 19-fold increased risk of the development of Alzheimer disease.¹⁴ Our preliminary observation regarding

ApoE3 and CTE will be tested by continuing ApoE genotyping of larger numbers of CTE-positive and -negative athletes. In 5 of our 17 cases (29%), we could not determine the ApoE genotypes. For these 5 cases, blood was not available for DNA extraction or repeated DNA extraction from formalin-fixed brain tissue failed. We recognize this as a limitation of our study and cohort. It is vital to note that ApoE genotyping is not mandatory and is not required for CTE neuropathologic diagnosis and histomorphologic phenotyping.

Our data are primarily based on forensic methodologies including forensic analyses of postmortem brain tissue obtained from autopsies. Premortem CTE syndromic profiles were obtained by forensic surrogate interviews of the next of kin and close family members of our CTE-positive cases. Although these are strengths of our cohort, they are also weaknesses; however, we are observing emerging syndromic profiles in our CTE-positive cases (Table 3). These profiles were in part previously published,^{3,5} and more studies are required to further confirm premorbid and premortem CTE clinicometrics.

CTE is distinct from mild cognitive impairment (MCI). MCI represents the earliest clinically detectable phase of dementia and Alzheimer disease. Elderly patients with MCI constitute a high-risk prodromal population at risk of dementia progression and development.^{23,24} The clinical signs and symptoms of CTE and MCI are different. Primarily, the MCI concept and diagnosis in the elderly require impairment in memory with preserved general cognitive functioning,²³ and hypertensive cerebrovascular disease is a frequent comorbidity of MCI.^{23,24} The neuropathologic findings in CTE and MCI are also different. The brains of those with MCI show topographically restricted neurofibrillary pathology limited to the entorhinal cortex, hippocampus, and amygdala accompanied by concomitant pathologic alterations, most frequently strokes, argyrophilic grains, and Lewy bodies.^{23,24} Neurofibrillary pathology in CTE does not exhibit the specific topographic restriction of MCI and is not accompanied by other concomitant alterations such as strokes or argyrophilic grains. There were no Lewy bodies in the brains of our CTE cohort.

As has been illustrated by our cases, CTE may coexist with other pathologic findings and diseases in the brain, which may be, pathogenetically or pathoetiologically, associated with CTE and may be defining features of other disease entities outside the defining features of CTE. In such instances, we recommend that these additional findings be enumerated as separate diagnoses accompanying CTE. For example, our case 14 exhibited pathologic changes that were consistent with CTE and other pathologic changes that were consistent with multicystic encephalopathy. For case 14, multicystic encephalopathy should be enumerated as a second diagnosis accompanying CTE diagnosis. The same applies to the identification of defining features of CTE and of other neurodegenerative diseases in the same brain of a decedent. For example, if defining α -synuclein inclusions for diffuse Lewy body disease are found along with defining CTE changes in the same brain, the 2 separate diagnoses, which should be enumerated, would be CTE and diffuse Lewy body disease.

Another example is the presence of defining ubiquitin inclusions for amyotrophic lateral sclerosis accompanying defining CTE changes in the brain of a decedent; the 2 diagnoses, which should be enumerated, would be CTE and amyotrophic lateral sclerosis. The enumeration of more than 1 neurodegenerative diagnosis in 1 decedent does not confirm causal, pathogenetic, or pathoetiologic associations; for instance, diffuse Lewy body disease pathology may accompany Alzheimer disease pathology in the brains of those with Alzheimer disease. In such instances, 2 separate diagnoses of Alzheimer disease and diffuse Lewy body disease are made without consolidating the 2 separate diseases into 1 diagnostic entity because they occur in the same decedent.⁹

Given the limited numbers of whole brains in our emerging cohort, we strongly recommend that CTE diagnosis and surveillance should no longer be regarded as empirical research requiring family consent. Rather CTE diagnosis and surveillance should become intrinsic components of routine patient care workups and routine hospital/medical examiner autopsies in high-risk cohorts like athletes. As a minimum standard and requirement, the whole brain of any deceased contact sport athlete should be routinely saved and examined by a neuropathologist for CTE diagnosis and surveillance as part of the standard protocols for determination of causes and manners of death, which is currently the standard practice for Parkinson disease, Alzheimer disease, and other neurodegenerative diseases.

We present emerging, recurring, and consistent histomorphologic CTE phenotypes that will facilitate CTE diagnosis and surveillance. These histomorphologic phenotypes may form the basis for future CTE classification schemes and may correlate with clinicometric phenotypes, which should be studied further.

Disclosure

The authors have no personal financial or institutional interest in any of the materials, drugs, or devices described in this article.

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COMMENTS

This study provides additional data to the sports-related chronic traumatic encephalopathy (CTE) literature, especially in the non-boxing population. The authors report that 1 of the 3 high school athletes had incipient CTE based on the following: none to very sparse (1 to several) neurofibrillary tangles and neuritic threads. Although neuropathologic, reference to incipient CTE in this case may result in readers prematurely concluding that sports-related head trauma can result in progressive encephalopathy in the high school population. Certainly, more research in this younger population needs to be conducted before this connection can be made. The authors also note that neuropsychiatric impairment observed in these athletes may be attributed to impairment of neuronal functioning by tauopathy and neuronal loss. Although possible, it is clear that other causes (alcohol, substance use) need to be considered in these cases.

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The study by Omalu et al concerns a hot topic related to the (risk of) repetitive brain injuries in American athletes. Although without doubt, it is important from a public health perspective to increase

awareness of such a possible risk, I question very much whether this article really serves this purpose. At best, the study can be considered controversial and I am concerned that the results reported in this study may be interpreted as providing further evidence in support of CTE as a high-risk entity in contact sports. The principal author previously published a number of case reports describing individual cases of CTE, and these cases are included in this cohort study. In this cohort study, the authors examine autopsy findings in 17 athletes whose brains were examined after unexpected deaths. In 11 of these, histomorphologic evidence consistent with the emerging diagnosis of CTE was described. The authors seem to claim more in the way that they present and discuss their results than the scientific findings can really offer.

The authors describe their case series as “our CTE cohort”. This erroneously suggests that all cases included were diagnosed as having CTE. Such is not the case: features consistent with CTE were only found in 11 of the 17 cases described. The results are limited to describing histomorphologic features on analysis of brain specimens without describing any clinical correlate. In fact, no evidence other than participation in sports activities is provided to support the assumption that the subjects had ever sustained some form of traumatic brain injury. Moreover, a case-control study is lacking; the authors only report on their own series, and the common denominators were that the subjects had died unexpectedly and had been engaged in high-level sports activities. The evidence linking the autopsy findings to repetitive injuries is at best indirect and cannot be considered conclusive. What would have made this study strong would be if the authors had also examined a control group of, for example, athletes from other sports in which repetitive brain injuries do not or only very seldom occur. We note that in the cohort study described, a total of 6 subjects had experienced traumatic brain injury in the past (cases 14 and 15) or as causative reason for the unexpected death (cases 3, 5, 16, 17). In addition, there were 4 cases of documented substance abuse in the current series. The possibility that chronic substance abuse that may even have occurred in more cases than only those who died of an overdose may lead to similar abnormalities cannot be excluded.

Whether the suggested histomorphologic phenotypes in this study may facilitate more objective surveillance and accurate identification of sentinel CTE cases as the authors hope is doubtful. Histologic analysis of the hippocampal region was not possible in 5 subjects, thus rendering conclusions on the relevance of presence or absence of abnormalities in the hippocampal region tentative at best. Criteria proposed for describing histomorphologic characteristics are often ambiguous; terms are used that are difficult to interpret and difficult to standardize (eg, none, none to sparse, sparse to frequent, moderate to frequent), without providing any guidance on how to score the frequency. This is fairly certain to induce considerable observer variation.

In summary, the primary asset of this study is limited to a hypothesis-generating nature. It does not meet scientific standards for any strong conclusions: there is no control group, no information is given on clinical signs and symptoms, no clinical correlate is described, and the only linkage to sports injuries is no more than very indirect. Nevertheless, it would be wrong to suppress publication of an emerging concept. It is up to the broad scientific community to judge the scientific merit of this concept, and of the current publication in particular, and future studies are needed to either prove or refute the validity of this concept. I just hope that the scientific community will be given the opportunity to pass such judgment and that science will not receive excessive media attention and influence.

Andrew I. R. Maas
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BAILES

EXHIBIT 5

Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide

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Following his discovery of chronic traumatic encephalopathy (CTE) in football players in 2002, Dr. Bennet Omalu hypothesized that posttraumatic stress disorder (PTSD) in military veterans may belong to the CTE spectrum of diseases. The CTE surveillance at the Brain Injury Research Institute was therefore expanded to include deceased military veterans diagnosed with PTSD. The authors report the case of a 27-year-old United States Marine Corps (USMC) Iraqi war veteran, an amphibious assault vehicle crewman, who committed suicide by hanging after two deployments to Fallujah and Ramadi. He experienced combat and was exposed to mortar blasts and improvised explosive device blasts less than 50 m away. Following his second deployment he developed a progressive history of cognitive impairment, impaired memory, behavioral and mood disorders, and alcohol abuse. Neuropsychiatric assessment revealed a diagnosis of PTSD with hyperarousal (irritability and insomnia) and numbing. He committed suicide approximately 8 months after his honorable discharge from the USMC. His brain at autopsy appeared grossly unremarkable except for congestive brain swelling. There was no atrophy or remote focal traumatic brain injury such as contusional necrosis or hemorrhage. Histochemical and immunohistochemical brain tissue analysis revealed CTE changes comprising multifocal, neocortical, and subcortical neurofibrillary tangles and neuritic threads (ranging from none, to sparse, to frequent) with the skip phenomenon, accentuated in the depths of sulci and in the frontal cortex. The subcortical white matter showed mild rarefaction, sparse perivascular and neuropil infiltration by histiocytes, and mild fibrillary astrogliosis. Apolipoprotein E genotype was 3/4. The authors report this case as a sentinel case of CTE in an Iraqi war veteran diagnosed with PTSD to possibly stimulate new lines of thought and research in the possible pathoetiology and pathogenesis of PTSD in military veterans as part of the CTE spectrum of diseases, and as chronic sequelae and outcomes of repetitive traumatic brain injuries. (DOI: 10.3171/2011.9.FOCUS11178)

KEY WORDS • posttraumatic stress disorder • Iraq •
chronic traumatic encephalopathy • suicide

IN 2002 Dr. Bennet Omalu²² discovered and described CTE in a football player when he performed an autopsy on Mike Webster. Since 2002, Dr. Omalu, the Brain Injury Research Institute, and other researchers have identified and described CTE in numerous football players, wrestlers, boxers, and ice hockey players, which have been reported in the literature.^{16,17,19–22,24,25} Following our elucidation of CTE in athletes, we hypothesized that PTSD in war veterans may belong to the CTE spectrum given that active military personnel are high-risk cohorts for repeated subconcussive and concussive trau-

matic brain injuries; for example, bomb blasts can cause traumatic brain injuries from primary pressure wave and acceleration-deceleration injury mechanisms.^{4,28} We expanded our CTE surveillance and brain tissue analyses to include deceased military veterans who were diagnosed with PTSD.

In 2010 we encountered CTE changes in the brain of a 61-year-old deceased Vietnam war veteran, who died suddenly as a result of coronary atherosclerotic disease. This case was reported in the *Stars and Stripes* news magazine of the Department of Defense.²⁶ The case was not published because we did not have comprehensive access to the medical records and family and social histories. Approximately 1 year later we have identified CTE changes in the brain of a 27-year-old Iraqi war veteran who was diagnosed with PTSD and committed suicide by hanging.

In our 2010 CTE paper,²⁰ we had defined CTE as

Abbreviations used in this paper: CTE = chronic traumatic encephalopathy; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; IED = improvised explosive device; PTSD = posttraumatic stress disorder; TDP-43 = TAR-DNA-binding protein 43; USMC = United States Marine Corps.

a progressive neurodegenerative syndrome caused by single, episodic, or repetitive blunt force impacts to the head and transfer of acceleration-deceleration forces to the brain. Chronic traumatic encephalopathy presents clinically after a prolonged latent period as a composite syndrome of mood disorders and neuropsychiatric and cognitive impairment. Direct brain tissue analysis reveals multifocal or diffuse tauopathy, which may be accompanied by low-grade and multifocal white matter rarefaction, microglial activation, and parenchymal histiocytes. Amyloidopathy may be present; however, the primary proteinopathy in CTE is a tauopathy. Some patients with CTE may not exhibit the classic prolonged latency period before clinical symptoms begin.

Posttraumatic stress disorder in war veterans was first designated in 1978 to describe a condition in Vietnam war veterans, and the syndrome was first recognized by the American Psychiatric Association in the early 1980s.³⁰ A primary neurodegenerative proteinopathy has not been defined for PTSD in war veterans. Pathognomonic tissue neuropathological features have not been specified. Clinical diagnoses are currently based on presenting clinical symptomatology, based on two diagnostic systems, which continue to evolve as our understanding of PTSD continues to grow.^{30,32} Table 1 shows the DSM-IV-TR clinical criteria for PTSD diagnosis,¹ and Table 2 shows the ICD-10 clinical criteria for PTSD diagnosis.³¹

We report this case as a sentinel case of CTE in an Iraqi war veteran diagnosed with PTSD to possibly stimulate new lines of thought and research in the possible pathoetiology and pathogenesis of PTSD in military veterans as it relates to PTSD being part of the CTE spectrum of diseases, and as chronic sequelae and outcomes of repetitive traumatic brain injuries.

Case Report

Premortem History

This subject was a 27-year-old Caucasian man who committed suicide by hanging approximately 8 months after his honorable discharge from the USMC and while he was beginning a divorce process with his wife. His wife for 3 years, a 6-year-old stepson, and a 2-year-old biological son had left him and moved in with her parents. Reportedly, he had performed well in high school, obtaining mostly "A" grades. In college he began binge drinking and barely received passing grades, which he attributed to his binge drinking; however, he received a bachelor's degree in history. Following college he joined the USMC at the age of 23 and was honorably discharged after 4 years (2006–2010) with a rank of corporal. Before entering the military he had worked as a waiter and as a staff member in a national vitamin retail chain.

His listed military occupational specialty was 1833 Amphibious Assault Vehicle Crewman. He served two deployments to Iraq. The first deployment to Iraq was in 2007 for approximately 8 months in Fallujah, where he was assigned to mechanized mobile patrols. The second deployment occurred in 2008 for approximately 5 months in Ramadi, where he was assigned to an entry control

point. He experienced combat and reported exposures to mortar blasts and IED blasts less than 50 m away. During the second deployment he was court marshaled twice for acting out, insubordination, fighting, hazing, and assault, and was dropped 1 rank. He described only a few incidents during his deployment that he found bothersome. There was an incident during the 3rd week of his first deployment when he witnessed a vehicle in his patrol blown up, and marines killed and wounded. In another incident, approximately 2 weeks later, while hooking up their disabled vehicle to tow, 2 marines in his section were shot and he helped to patch them up. In yet another incident, he witnessed a school bus full of Iraqi citizens, many of whom were children, blown up by an IED.

After his deployments he was stationed at a base and played football in a base league. During a football game in 2009, approximately 9 months after his second deployment, he reported being hit from the side causing him to fall to the ground. He stood up, stumbled, fell again, and then continued the game. Other players noticed that he was confused and kept asking the count and details of the next play and he had to be removed from the game. The events of the following week were unclear and he reported residual headaches and memory problems. Reportedly a conventional CT scan of the head was performed and showed no significant findings. He reported playing football and hockey for leisure and was never diagnosed with a concussion, although he suffered his "bell rung."

Two days prior to a 2010 neuropsychological evaluation, he was involved in a single motor vehicle crash while he was driving under the influence of alcohol, when he turned a corner and flipped his car. He woke up later hanging upside down in the car. It was not clear whether he lost consciousness from a head injury or from stuporous alcohol intoxication. He noted the following morning that he suffered from headaches and vomited; however, it was not also clear whether these symptoms were alcohol-related or head injury-related. He lost his driver's license after this crash for driving under the influence and refusing a blood-alcohol test. He visited a Veteran Affairs Medical Center the day before he committed suicide and reported having a new job as a football coach with his old high school, and was currently attending a community college. His driving under the influence charges had been dismissed.

In 2010, he was referred for a neuropsychological screening. His wife reported that he forgot dates, conversations, and trivialities of daily living. He also forgot whether he completed tasks, and sometimes confused his wife's and sister's names. He had problems making decisions and therefore avoided them. He believed he snapped at his children too frequently and was increasingly becoming a grumpy person. He admitted to headaches that occurred 3 to 4 times per week, which he described as pressure in his entire head. The headaches were relieved by a nonsteroidal antiinflammatory agent. He experienced bilateral hearing problems and tinnitus, which he dated back to when he had worked on engines in the military. He reported dizziness when he woke up at night to use the bathroom, slept only 4 hours a night, and had trouble falling asleep. Other reported symptoms included irrita-

Chronic traumatic encephalopathy in an Iraqi war veteran

TABLE 1: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), Fourth Edition: Diagnostic Criteria for Posttraumatic Stress Disorder*

-
- A. The person has been exposed to a traumatic event in which both of the following were present:
1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
 2. The person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior
- B. The traumatic event is persistently reexperienced in 1 [or more] of the following ways:
1. Recurrent and intrusive distressing recollections of the event including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are exposed.
 2. Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.
 3. Acting or feeling as if the traumatic event were recurring [includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated]. Note: In young children, trauma-specific reenactment may occur.
 4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
 5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
- C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by 3 (or more) of the following:
1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
 2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
 3. Inability to recall an important aspect of the trauma
 4. Markedly diminished interest or participation in significant activities
 5. Feeling of detachment or estrangement from others
 6. Restricted range of affect (e.g., unable to have loving feelings)
 7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)
- D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by 2 (or more) of the following:
1. Difficulty falling or staying asleep
 2. Irritability or outbursts of anger
 3. Difficulty concentrating
 4. Hypervigilance
 5. Exaggerated startle response
- E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.
- F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Specify if:
- Acute: if duration of symptoms is less than 3 months
- Chronic: if duration of symptoms is 3 months or more
- Specify if:
- With Delayed Onset: if onset of symptoms is at least 6 months after the stressor
-

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bility, discomfort with crowds, startle reactions, anhedonia, withdrawal and lack of engagement with the family, emotional numbing, and detachment. Many of his symptoms began after his first and second deployments. He also reported getting angry quickly and losing his temper frequently. He smoked cigarettes and reported drinking rarely; however, when he did drink, he drank a lot. When he got out of the marines he drank weekly. There was minor experimentation with marijuana and other drugs while he was in college. He was not aware of any family history of mental illness or any developmental impairment. His other significant medical history was a nasal bone fracture from an unspecified cause when he was 21 years old.

Neuropsychological Testing

The following neuropsychological tests and procedures were performed: Wechsler Test of Adult Intelligence; California Verbal Learning Test; Rey-Osterrieth Complex Figure Test; Grooved Pegboard Test; Finger Tapping Test; Trail Making Test; Word-list generation tasks; Ruff Figural Fluency Test; Ruff 2&7 Selective Attention Test; Test of Memory Malingering; Beck Depression Inventory-2; and PTSD checklist-military version.

For general cognitive functioning, his baseline intellectual abilities were estimated to fall in the high average to superior range based on demographic variables as well as a word-reading test (Wechsler Test of Adult Intel-

TABLE 2: World Health Organization ICD-10 classification of mental and behavioral disorders. Clinical descriptions and diagnostic guidelines***PTSD**

This arises as a delayed and/or protracted response to a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone (e.g., natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime). Predisposing factors such as personality traits (e.g. compulsive, asthenic) or previous history of neurotic illness may lower the threshold for the development of the syndrome or aggravate its course, but they are neither necessary nor sufficient to explain its occurrence.

Typical symptoms include episodes of repeated reliving of the trauma in intrusive memories ("flashbacks") or dreams, occurring against the persisting background of a sense of "numbness" and emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities and situations reminiscent of the trauma. Commonly there is fear and avoidance of cues that remind the sufferer of the original trauma. Rarely, there may be dramatic, acute bursts of fear, panic or aggression, triggered by stimuli arousing a sudden recollection and/or re-enactment of the trauma or of the original reaction to it.

There is usually a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia. Anxiety and depression are commonly associated with the above symptoms and signs, and suicidal ideation is not infrequent. Excessive use of alcohol or drugs may be a complicating factor. The onset follows the trauma with a latency period, which may range from a few weeks to months (but rarely exceeds 6 months). The course is fluctuating but recovery can be expected in the majority of cases. In a small proportion of patients the condition may show a chronic course over many years and a transition to an enduring personality change.

Diagnostic Guidelines

This disorder should not generally be diagnosed unless there is evidence that it arose within 6 months of a traumatic event of exceptional severity. A "probable" diagnosis might still be possible if the delay between the event and the onset was longer than 6 months, provided that the clinical manifestations are typical and no alternative identification of the disorder (e.g., as an anxiety or obsessive-compulsive disorder or depressive episode) is plausible. In addition to evidence of trauma, there must be a repetitive, intrusive recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feeling, and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioural abnormalities all contribute to the diagnosis but are not of prime importance.

* Reprinted with permission from the WHO.

ligence: estimated full-scale intelligence quotient = 119, 90th percentile). For attention, he was able to attend to instructions throughout the evaluation. He occasionally required some limited repetition of directions. A measure of selective attention was in the average range for speed (58th percentile) and accuracy (62nd percentile). His performance improved slightly as the test progressed, which suggested intact sustained attention to the task. For cognitive/motor processing speed, connection of sequentially numbered circles was performed in the average range (25 seconds, 42nd percentile). Fine motor dexterity was in the average range bilaterally. The dominant-hand performance was 1 second slower than the nondominant hand (right 61 seconds, 42nd percentile; left 60 seconds, 69th percentile).

For executive functioning, a task that required the ability to establish and maintain an alternating alphanumeric sequence was performed in the average range (49 seconds, 58th percentile) with no errors. Word-list generation by letter was in the superior range (FAS = 17/18/25, 92nd percentile), while generation by category was high-average (28 animals, 76th percentile). Design fluency was in the low-average range (14th percentile), with a few repetition errors (5 total, 42nd percentile). Approach on the first trial was efficient and productive, but his efficiency declined on the subsequent 4 trials, resulting in a lower total output. Copy of a complex design was impaired (less than first percentile), due largely to a highly segmented approach with no attention to the gestalt of the figure.

For learning and memory, his ability to learn a list

of 16 words over 5 consecutive learning trials was in the average range (California Verbal Learning Test-2, 42nd percentile). His performance on a subsequent interference list was in the superior range (93rd percentile), reflecting a benefit from prior exposure to analogous task. Free recall following this interference list was in the average range (12 words, 69th percentile). Cuing did not change his performance (50th percentile). After a longer delay, his recall was at the 31st percentile, and with cuing, at the 14th percentile. He committed 11 intrusion errors across trials (second percentile): about half were the same single word, which he listed on each learning trial and 1 recall trial, and the remainder represented source memory errors. Yes/no recognition revealed a positive response bias (15/16 hits, 50th percentile; 6 false positive errors, most of which were source-recognition errors and all of which were semantically related, 7th percentile). Forced-choice recognition was errorless (16/16). Incidental memory for a complex design was in the impaired range for both immediate (second percentile) and delayed (first percentile) conditions, likely due in large part to his aforementioned fractured approach to the initial copy of the figure.

Diagnosis of PTSD

His final diagnoses were the following: Axis 1: PTSD with hyperarousal (irritability and insomnia) and numbing, alcohol abuse, continuous; Axis 2: deferred; Axis 3: hyperlipidemia; Axis 4: combat deployment, reintegration difficulties, unemployment, recent arrest, marital stress. His prescribed neurotropic medications included

Chronic traumatic encephalopathy in an Iraqi war veteran

citalopram, trazodone, and prazosin. In a clinic visit 2 months prior to his suicide, he reported persistent PTSD symptoms.

Postmortem History

The subject's parents had requested the police perform a well-being check of their son after they had not heard from him for 2 days. The police found our subject in his residence hanging from a staircase by a leather belt noose around his neck. A full forensic autopsy by the combined technique of Virchow and Rokitansky¹⁴ was performed by the medical examiner. After informed consent was granted by the wife and next-of-kin, his brain was forwarded to the Brain Injury Research Institute for gross neuropathological, histochemical, and immunohistochemical analysis.

Autopsy Findings

At autopsy our subject was unclad, appeared well-developed and well-nourished, weighed approximately 211 pounds, measured approximately 74 inches, and appeared consistent with the stated age of 27 years old. There was a ligature, which was tightly wound around the neck in a noose, and composed of a brown braided leather belt, which was looped through a buckle located on the posterior neck. The underlying ligature indentation mark was situated circumferentially around the neck in a transverse-oblique-ascending fashion. There were no anterior strap muscle hemorrhages or fractures of the hyoid bone or thyroid cartilage.

Dissection of the thoracic and abdominal cavities revealed normally situated viscera, which were grossly and histologically unremarkable. The scalp revealed no contusional hemorrhages. Dissection of the cranial cavity revealed no skull fractures and no intracranial hemorrhages. Toxicological analysis of the fluoridated heart blood and vitreous humor revealed the presence of citalopram only without any other drug detected. A sample of whole heart blood was submitted for apolipoprotein E genotyping in an ethylenediaminetetraacetic acid specimen bottle. The underlying cause of death was determined to be asphyxiation due to hanging and the manner of death was determined to be a suicide.

Gross Neuropathological Findings

The brain was fixed in 10% buffered formaldehyde for 2 weeks before it was grossed. The dura mater revealed no xanthochromia, membranes, or hemorrhages. The weight of the formaldehyde fixed brain was 1624 grams. The cerebral and cerebellar hemispheres appeared symmetrical and exhibited gyral, sulcal, and folial convolutions that appeared normal. There was diffuse global and symmetrical expansion of gyri and compression of sulci, accompanied by symmetrical bilateral grooving of the unci and cerebellar tonsils, with symmetrical compression of the subarachnoid cisterns. The arachnoid and pia mater appeared smooth and glistening without acute or chronic subarachnoid hemorrhages. There was no acute or chronic cerebral cortical contusional or ischemic necrosis or hemorrhage. There was no lobar cortical atrophy.

The centrum semiovale and the periventricular white matter revealed very focal decompositional change and Swiss-cheese appearance, accompanied by central red-pink parenchymal discoloration, edema, and congestion. There was no periventricular leukomalacia, demyelinating plaques, necrosis, hemorrhage, or infarct in the subcortical white matter. There was no acute or chronic gliding contusional hemorrhage or necrosis.

The ventricles were symmetrically compressed and showed no acute or chronic intraventricular hemorrhage. The genu, body, and splenium of the corpus callosum revealed no hemorrhages or necrosis. All subcortical nuclei, including the caudate nucleus, putamen, globus pallidus, thalamus, and subthalamic nucleus, on both sides, revealed no atrophy, necrosis, or hemorrhage (Fig. 1 upper). The hippocampus and parahippocampal gyrus, on both sides, were not dysplastic or atrophic (Fig. 1 lower).

The midbrain, pons, and medulla oblongata revealed no atrophy, dorsolateral hemorrhage, or collicular and teg-

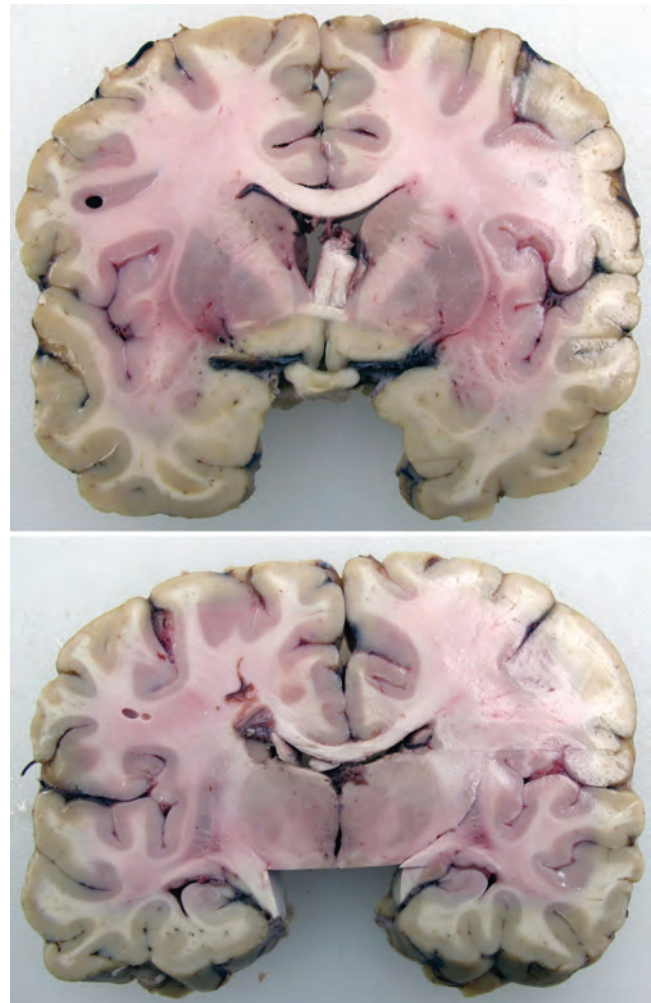


FIG. 1. Gross photographs of the coronal section of the brain at the level of the anterior commissure (upper) and hippocampus (lower), showing diffuse parenchymal edema with very focal Swiss-cheese change, without atrophy of the subcortical ganglia (upper), hippocampus or thalamus (lower), or any other focal gross parenchymal gray or white matter lesions.

mental necrosis or hemorrhage. The basis pontis showed no central myelinolysis or Duret hemorrhage. The cerebral peduncles, medullary pyramids, and cerebellar peduncles were not atrophic and showed no hemorrhage or necrosis. The substantia nigra and locus ceruleus were adequately pigmented for age. The inferior olivary nuclei and dentate nuclei revealed normal convolutional patterns. The cerebellar hemispheres revealed no folial atrophy or necrosis. There were no hemorrhages or infarcts in the cerebellar cortex or white matter. The pituitary gland appeared unremarkable. The spinal cord revealed no epidural, subdural, or subarachnoidal hemorrhage. The spinal medulla appeared unremarkable without segmental atrophy, contusional necrosis or hemorrhage, or white matter funicular degeneration or demyelination.

Thirty-one representative topographically selected sections of the dura mater, neocortex, subcortical ganglia, brainstem, pituitary gland, and spinal cord were obtained and stained by the following histochemical and immunohistochemical tissue staining protocols: 1) H & E; 2) tau; 3) β -A4 amyloid; 4) α -synuclein; 5) glial fibrillary acidic protein; 6) CD-68; 7) Luxol fast blue and cresyl violet; 8) ubiquitin; 9) TDP-43; and 10) Bielschowsky silver impregnation stain.

Microscopic Neuropathological Findings

H & E Stains. The frontal, parietal, temporal, occipital, insular, and cingulate cortex revealed the expected columnar and laminar organization without cortical disorganization or dysplasia. There was negligible-to-mild neuronal dropout without eosinophilic neuronal necrosis. There was diffuse perineuronal vacuolation, expansion of Virchow Robin spaces and patchy neuropil microspangiosis of both the gray and white matter. There was marked congestion of the arachnoid and pia mater and the penetrating parenchymal vessels. Multifocal sparse perivascular pigment-laden histiocytes were noted in many Virchow Robin spaces.

The body and splenium of the corpus callosum, internal, external, and extreme capsules revealed no necrosis, hemorrhage, rarefaction, myelinolysis, or axonolysis. The periventricular white matter revealed no leukomalacia or subependymal astrogliosis. The subcortical ganglia including the caudate nucleus, putamen, globus pallidus, hypothalamus, thalamus, amygdala, and basal nucleus of Meynert showed only diffuse neuropil extracellular edema. There was no mineralization of the walls of the vessels of the globus pallidus or cornu ammonis.

The dentate gyrus, cornu ammonis, subiculum, and entorhinal cortex of the hippocampus revealed no significant neuronal dropout, dysplasia, or sclerosis. There was no eosinophilic necrosis of the pyramidal neurons of the stratum pyramidalis. The midbrain, pons, and medulla revealed parenchymal edema without any other focal or diffuse lesions. The neurons of the substantia nigra, locus ceruleus, and dorsal raphe nucleus were adequately pigmented and revealed no neuronal dropout, Marinesco bodies, pale bodies, or Lewy bodies. The cerebellar cortex revealed negligible Purkinje neuron dropout and Bergmann astrogliosis. The internal granule cell layer and

dentate nucleus were unremarkable. The cerebellar white matter revealed no rarefaction, necrosis, or infarcts. The dura mater revealed marked intradural congestion without inflammation, or acute or remote hemorrhage. The adenohypophysis revealed focal interstitial fibrosis and marked sinusoidal congestion. The neurohypophysis was congested and edematous. The spinal medulla revealed the normal gray and white matter morphology without significant loss of the anterior horn neurons, which showed sparse non-specific cytoplasmic neuronal changes. The white matter funiculi and tracts were unremarkable.

Other Histochemical and Immunohistochemical Stains. Tau-immunostained sections revealed none, to sparse, to multifocally frequent band- and flame-shaped neurofibrillary tangles and neuritic threads in the frontal cortex, parietal cortex, temporal cortex, occipital cortex, and cingulate cortex with a skip phenomenon,²⁰ accentuated in the depths of sulci (Fig. 2). The largest numbers of tangles and threads were noted in the frontal cortex, with none in the occipital cortex. The CA1 region and subiculum revealed none to sparse flame, band, and small globose neurofibrillary tangles and neuritic threads. The entorhinal cortex revealed moderate band- and flame-shaped neurofibrillary tangles and neuritic threads. There was focally sparse to moderate flame- and band-shaped neurofibrillary tangles in the amygdala. The CA2, CA3, and CA4 regions of the cornu ammonis showed no neurofibrillary tangles in the pyramidal neurons and no neuritic threads. The granule neurons of the dentate fascia revealed no neurofibrillary tangles or neuritic threads. There was focally sparse flame- and band-shaped neurofibrillary tangles and neuritic threads in the anterior perforated substance and basal nucleus of Meynert. The thalamus and hypothalamus showed several large globose neurofibrillary tangles and neuritic threads. The substantia nigra showed none to sparse small and large globose neurofibrillary tangles and neuritic threads. The caudate nucleus, insula cortex, putamen, and globus pallidus revealed no neurofibrillary tangles. Only 1 neuritic thread was noted in the globus pallidus. There were no neurofibrillary tangles in the midbrain tegmentum. Few pretangles were noted in neurons of the periaqueductal gray matter. The ventral tegmental pons revealed a single large globose neurofibrillary tangle and several neuritic threads. A single neuron revealed a globose neurofibrillary tangle in the locus ceruleus, accompanied by several neuritic threads. The medullary tegmentum and the inferior olivary nuclei revealed no neurofibrillary tangles or neuritic threads. The Purkinje neurons, internal granule neurons, and the dentate neurons of the cerebellum revealed no neurofibrillary tangles. The anterior horn neurons of the spinal cord revealed no neurofibrillary tangles. There were no neuritic threads in the spinal gray or white matter. Tufted astrocytes, thorn astrocytes, astrocytic plaques, and astrocytic coils and grains were absent in all sections of the brain examined.

There was focal ubiquitin immunopositivity of few neurofibrillary tangles and neuritic threads, otherwise there were no ubiquitin neuronal or glial inclusions in all sections of the brain examined. There were no diffuse or

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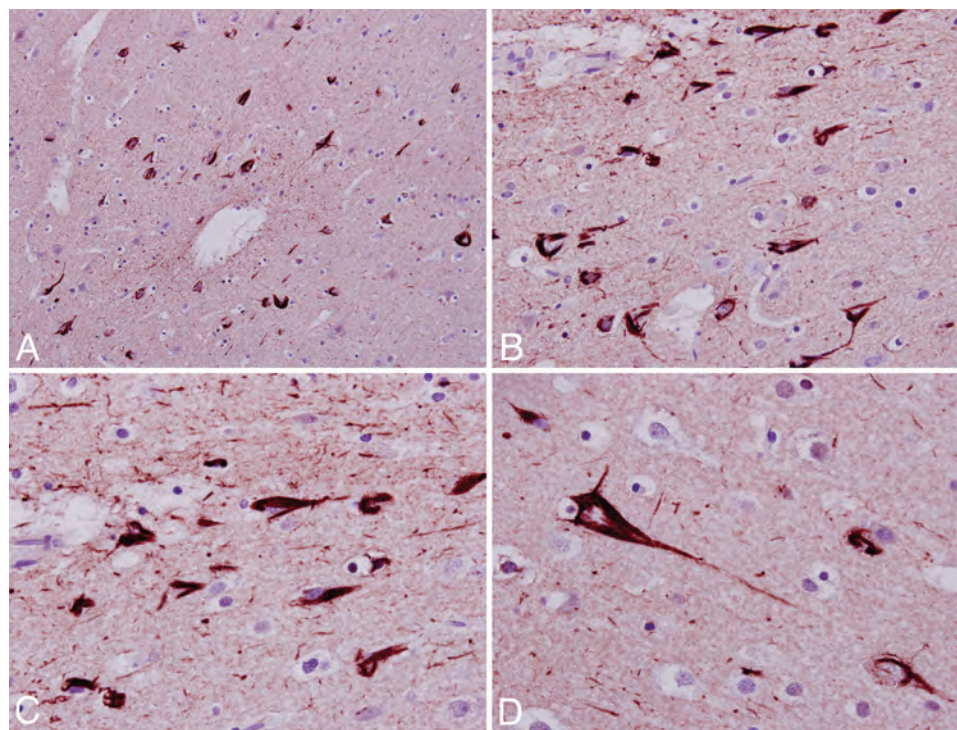


Fig. 2. Photomicrographs of tau-immunostained section of the frontal cortex showing frequent neurofibrillary tangles and neuropil threads (A and B), with higher magnification (C and D) showing band- and flame-shaped neurofibrillary tangles and neuropil threads. Original magnification $\times 200$ (A), $\times 400$ (B), $\times 600$ (C and D).

neuropil amyloid plaques and no cerebral amyloid angiopathy in all examined sections of the cortex, hippocampal formation, subcortical ganglia, brainstem, cerebellum, and spinal medulla. There were no Lewy bodies, Lewy neuritis, or glial alpha-synuclein inclusions in all examined sections of the cortex, hippocampal formation, subcortical ganglia, brainstem, cerebellum, and spinal medulla.

Glial fibrillary acidic protein immunostains revealed multifocal mild perivascular fibrillary astrogliosis and activation of astrocytes in the gray cortex and molecular layer of the frontal cortex, cingulate cortex, parietal cortex, temporal cortex, and occipital cortex. The subcortical gyral white matter of the cortical lobes revealed multifocal and superficial white matter fibrillary astrogliosis and activation of astrocytes. The body and splenium of the corpus callosum showed multifocal and mild fibrillary astrogliosis and activation of astrocytes. There was mild diffuse fibrillary astrogliosis of the hippocampus including the dentate fascia and gyrus, alveus, strata oriens, radiatum, lacunosum, and moleculare. There was mild diffuse astrogliosis of the thalamus, midbrain, pons, and medulla oblongata. There was diffuse astrogliosis of the neurohypophysis. The cerebellum revealed Bergmann astrogliosis with multifocal fibrillary astrogliosis of the superficial folial cerebellar white matter. There was mild diffuse fibrillary astrogliosis of the hypothalamus, amygdala, and anterior perforated substance (basal nucleus of Meynert). The anterior, lateral, and posterior cervical, thoracic, and lumbar funiculi did not show any remarkable astrogliosis.

The CD-68-immunostained sections of the frontal cortex, parietal cortex, temporal cortex, occipital cortex,

cingulate gyrus, caudate nucleus, insula cortex, putamen, thalamus, hypothalamus, globus pallidus, cerebellum, corpus callosum, midbrain, pons, and medulla revealed nonspecific multifocal lysosomal astrocytic and microglial staining, accompanied by multifocal immunopositive staining of scattered perivascular histiocytes in and around the Virchow Robin spaces. Small clusters of neuropil histiocytes were present multifocally accentuated in the frontal and parietal subcortical white matter, internal capsule, anterior body of the corpus callosum, splenium of the corpus callosum, anterior commissure, cerebral peduncles, and transverse and longitudinal fascicles of the basis pontis. Similar changes were also noted in the cervical, thoracic, and lumbar anterior, lateral, and posterior funiculi, as well as in the amygdala and anterior perforated substance.

The sections stained with Luxol fast blue and cresyl violet from the frontal, temporal, parietal, and occipital cortex revealed mild diffuse rarefaction of the subcortical white matter, relatively sparing the occipital cortex, and accentuated in the frontal and parietal cortex. There was mild to moderate rarefaction of the subcortical white matter of the cingulate cortex, periventricular white matter of the lateral angle of the lateral ventricle, and of the anterior corpus callosum, as well as of the anterior commissure. There was diffuse mild rarefaction of the internal, external, and extreme capsules. Minimal rarefaction of the cerebral peduncle and medullary pyramids was noted. There was mild to moderate rarefaction of the transverse and longitudinal fasciculi of the basis pontis. There was no rarefaction of the deep cerebellar white matter. The splenium of the corpus callosum revealed mild rarefac-

tion. There was no rarefaction or myelinolysis of the spinal anterior, lateral, or posterior funiculi.

The TDP-43–immunostained sections of the left frontal cortex, parietal cortex, cingulate cortex, insula cortex, claustrum, caudate nucleus, putamen, globus pallidus, and thalamus revealed very sparse and focal TDP-immunopositive cytoplasmic and neuritic inclusions in the frontal cortex and caudate nucleus. The pyramidal neurons of the cornu ammonis and the granule neurons of the dentate fascia revealed no TDP proteinopathy. The midbrain tegmentum, colliculi, periaqueductal gray matter, and substantia nigra showed very sparse and focal TDP nuclear and cytoplasmic inclusions in the substantia nigra. The Purkinje cell layer, internal granule cell layer, and dentate nucleus revealed no TDP proteinopathy or cytoplasmic inclusions. The anterior horn neurons of the spinal medulla revealed sparse and focal nuclear TDP inclusions accompanied by sparse dystrophic TDP-positive neurites.

The specified constellation of gross neuropathological, histomorphological, and immunophenotypical findings in this case are consistent with changes we have described and identified in CTE in American athletes.²⁰

Apolipoprotein E Genotyping

Apolipoprotein E genotyping was performed using genomic DNA extracted from peripheral blood leukocytes in whole autopsy blood using the QIAamp DNA Blood Mini kit (Qiagen). The apolipoprotein E genotype was ascertained from the amplified DNA by fluorogenic 5' nuclease assays (TaqMan SNP genotyping assays; Applied Biosystems). The apolipoprotein E genotype was 3/4.

Discussion

In this report we present the sentinel case of a 27-year-old Iraqi war veteran who was formally diagnosed with PTSD, committed suicide by hanging, and whose brain at autopsy revealed gross, histomorphological, and immunophenotypical findings that we have identified and described in CTE in American athletes.²⁰ As in our previous CTE cases,^{19–25} the primary proteinopathy we identified was a tauopathy in the form of multifocal sparse to frequent topographic neurofibrillary tangles and neuritic threads with a skip phenomenon.²⁰ Focal secondary TDP proteinopathy was identified. Nonspecific white matter changes accompanied the tauopathy, consisting of nonspecific fibrillary astrogliosis, white matter rarefaction, and perivascular and neuropil infiltration by histiocytes. There was no significant cortical, subcortical, or hippocampal cerebral atrophy. Acute or chronic focal traumatic brain injuries such as lobar contusional necrosis or hemorrhages were absent.

Apolipoprotein E genotype in this case was 3/4. The E3 allele is the most recurrent apolipoprotein E allele we are observing in our CTE cohort,²⁰ although our sample sizes are small and this observation is preliminary. We currently have no conclusive explanation for this trend that we are observing because the apolipoprotein E4 allele has been reported to be the high-risk allele for Alzheimer disease and adverse outcomes of traumatic brain injury.^{2,8} However, we suspect that E4 may not be the pri-

mary apolipoprotein E risk allele for CTE although it has been suggested to be associated with chronic traumatic brain injury and cognitive impairment in boxers and professional football players.^{11,13,29} Kristman et al.,¹² however, did not find any important association between the E4 allele and the risk of sustaining a concussion in amateur collegiate athletes.

Our subject was a member of a population cohort that can be exposed to repetitive traumatic brain injuries. Traumatic brain injury has been referred to as the signature injury of Operation Enduring Freedom and Operation Iraqi Freedom. It has been estimated that 15%–30% of troops engaged in active combat in Afghanistan and Iraq have suffered concussions and subconcussions, many as a result of blasts from explosive devices. The majority of these patients manifest neuropsychiatric symptoms and cognitive impairments beginning immediately after the injury and lasting for days to weeks to months. Approximately 18%–30% of these patients develop persistent, progressive, and sometimes disabling constellations of neuropsychiatric and cognitive impairments, which are interpreted to represent PTSD.³ Our subject also played football and hockey for leisure and suffered a remote nasal bone fracture. It is our belief that his eventual CTE risk outcome occurred as a result of his lifetime and cumulative exposure to repeated subconcussive and concussive traumatic brain injuries, with his military exposures being the primary injuries that precipitated CTE.

Our subject manifested persistent symptoms of CTE or PTSD and eventually committed suicide by hanging. We have previously associated parasuicides and suicides with CTE²¹ and are observing an overrepresentation of suicides and drug-related accidental deaths in our CTE cohort.²⁰ According to a 2010 Department of Defense report,⁶ the suicide rates in all services increased from about 10 per 100,000 people in 2001 to about 20 per 100,000 people in 2009, while the suicide rate in the general US population remained at approximately 11.5 per 100,000 in 2007. The propositional question that this sentinel case report raises is: What role does CTE play in the increasing incidence of suicides in the US military? This question can only be answered by more forensic observational and translational research focused on CTE and suicides in military veterans.

Members of the armed forces can sustain repetitive traumatic brain injury from training activities, from noncombat professional activities, and from combat activities. Blast exposure is the most common cause of traumatic brain injury in the wars in Iraq and Afghanistan.⁷ Explosives like mortar shells, rocket-propelled grenades, and IEDs cause blast injuries via complex physical events, which have the potential to precipitate repetitive subconcussive and concussive brain injuries. The mechanisms of brain damage are not yet well understood, but several neurotrauma mechanisms have been proposed.^{4,7,27}

While emphasizing that no human autopsy studies, conducted with current immunohistochemical methods, have been published on blast-related traumatic brain injury in the military, Mac Donald et al.,¹⁵ using diffusion tensor imaging, concluded that blast exposure in US military personnel causes traumatic axonal injury. Follow-up

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diffusion tensor imaging 6 to 12 months after preliminary postexposure diffusion tensor imaging confirmed persistence of traumatic axonal injury abnormalities in the brains of their military subjects. Their conclusions and findings support the conclusions, interpretations, and propositional sentinel value of this case report. The primary proteinopathy in CTE is hyperphosphorylated tau, which is a microtubule-associated protein that is involved in the pathophysiological cascades of traumatic axonal injury.¹⁰ We observed nonspecific white matter changes in this case, which accompanied tauopathy.

In addition to tauopathy in this case, we observed a focal and sparse secondary TDP proteinopathy. Such a TDP proteinopathy frequently occurs as a nondiagnostic or nondefining accompaniment and secondary proteinopathy of a variety of primary proteinopathies in a broad spectrum of neurodegenerative diseases, including Alzheimer disease.^{5,9,18} Secondary proteinopathies in neurodegenerative diseases is a frequent occurrence, and CTE, as a trauma-induced neurodegenerative disease, may be accompanied by secondary proteinopathies in different cases of CTE.

Conclusions

In this paper we present the case of a 27-year-old USMC Iraqi war veteran who developed persistent impaired neuropsychiatric and cognitive functioning, and mood disorders, following deployments to Iraq and an honorable discharge. He was clinically diagnosed with PTSD and prescribed neurotropic drugs. He eventually committed suicide by hanging. Autopsy, as well as gross and histomorphological examination of his brain, revealed CTE changes similar to the CTE changes we have observed in American athletes. Chronic traumatic encephalopathy is the cumulative outcome of repeated subconcussive and concussive brain injuries, and in this instance, it is our opinion that the decedent sustained repeated subconcussive and concussive brain injuries primarily from exposures from blasts and secondarily from training activities and noncombat activities as a marine. Other possible tertiary nonmilitary contributory factors to his cumulative risk of developing CTE may have included a remote traumatic history of nasal bone fracture and engagement in contact sports such as football and hockey for leisure. This sentinel case highlights the need for forensic, observational, and translational research to further confirm that a proportion of PTSD cases in war veterans may be due to, or contributed to by, CTE caused by repeated subconcussive and concussive traumatic brain injuries.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Omalu, Hammers, Bailes, Fitzsimmons. Acquisition of data: Omalu, Hammers, Hamilton, Kamboh, Webster. Analysis and interpretation of data: Omalu, Hamilton, Kamboh. Drafting the article: Omalu. Critically revising the article: Omalu, Hammers, Bailes, Fitzsimmons.

Reviewed submitted version of manuscript: Omalu, Hammers, Bailes, Webster, Fitzsimmons. Approved the final version of the manuscript on behalf of all authors: Omalu. Administrative/technical/material support: all authors. Study supervision: Omalu, Bailes, Fitzsimmons.

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BAILES EXHIBIT 6

PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

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Objective: Mild traumatic brain injury due to contact sports may cause chronic behavioral, mood, and cognitive disturbances associated with pathological deposition of tau protein found at brain autopsy. To explore whether brain tau deposits can be detected in living retired players, we used positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP). **Methods:** Five retired National Football League players (age range: 45 to 73 years) with histories of mood and cognitive symptoms received neuropsychiatric evaluations and FDDNP-PET. PET signals in subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal) regions were compared with those of five male controls of comparable age, education, and body mass index. **Results:** FDDNP signals were higher in players compared with controls in all subcortical regions and the amygdala, areas that produce tau deposits following trauma. **Conclusions:** The small sample size and lack of autopsy confirmation warrant larger, more definitive studies, but if future research confirms these initial findings, FDDNP-PET may offer a means for premorbid identification of neurodegeneration in contact-sports athletes. (Am J Geriatr Psychiatry 2013; 21:138–144)

Key Words: Positron emission tomography, FDDNP, tau, amyloid, mood disorder, depression, mild cognitive impairment, dementia

According to recent CDC estimates, 1.6–3.8 million sports-related traumatic brain injuries (TBIs) occur each year, including those never

reported to healthcare professionals.¹ Most are minor concussions; many are repeated injuries and subconcussive blows.¹

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Repetitive mild TBI due to contact sports may lead to chronic mood, behavioral, and cognitive changes.² Studies of retired contact-sport athletes, such as National Football League (NFL) players, show a higher rate of personality, behavioral, and mood disturbances (e.g., depression, irritability, impulsiveness), mild cognitive impairment (MCI, a risk state for dementia), and dementia compared with controls. Professional athletes exposed to repetitive mild TBIs are prone to develop chronic impairment, and available evidence suggests a possible dose response.³ Retired NFL players with three or more reported concussions during their career were three times more likely to be diagnosed with depression and five times more likely to be diagnosed with MCI.^{3,4}

Several investigators have described chronic traumatic encephalopathy (CTE), a clinicopathological entity that includes mood, personality, cognitive, and behavioral changes (e.g., suicidality), and motor symptoms (e.g., abnormal gait, tremor) associated with a range of autopsy findings, particularly widespread accumulation of phosphorylated tau protein as neurofibrillary tangles (similar to those observed in Alzheimer disease), astrocytic tangles, neurites, diffuse axonal injury, white matter abnormalities, inflammation, and immune proinflammatory cytokine responses in traumatized brain regions.⁵ Immunoreactive deposits are found in neocortical, subcortical (e.g., thalamus, caudate, putamen, midbrain, and cerebellar white matter), and medial temporal (hippocampus, entorhinal cortex, and amygdala) regions, where neuronal loss may be observed.⁵ TDP-43 proteinopathy may accompany tauopathy in CTE cases and is more prominent in motor neuron disease cases.⁶ Amyloid deposition has been reported in approximately 40% of CTE cases and generally consists of diffuse plaques with relatively few cortical neuritic plaques.⁵ Currently, CTE in former football players is only diagnosed at autopsy.

Our group invented 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP)-positron emission tomography (PET) for measuring both tau tangle and amyloid plaque deposition in living brains.⁷ FDDNP signals differentiate Alzheimer disease from MCI and normal aging and predict future cognitive decline in nondemented subjects.^{8,9} Although other tau tracers have been tested in human brain tissue sections and animal models,^{10,11} FDDNP is the only PET probe of

tau that has been studied in vivo in human imaging trials. FDDNP is not specific for tauopathies, but previous autopsy follow-up studies indicate regional specificity in patients with Alzheimer disease, wherein FDDNP-PET shows high signals in medial temporal regions where autopsy studies indicate a preponderance of tau tangles, as well as high signal in lateral temporal regions, where amyloid plaques are highly concentrated.⁸

Despite the devastating consequences of TBIs due to contact sports and the large number of people at risk, no method for early detection of such pathology has yet been established. To address this issue, we performed PET scans after intravenous injections of FDDNP to explore whether brain tau deposits could be detected in a small group of retired NFL players with cognitive and mood symptoms and compared them with a group of male controls of comparable age, educational achievement, and body mass index (BMI).

METHODS

Neuropsychiatric evaluations were performed on five retired players aged 45 years or older who were recruited for this study because of a history of cognitive or mood symptoms. Through organizational contacts, NFL retirees with MCI-like symptoms were referred for testing. Of the 19 potential volunteers, 14 did not participate because of non-response or disinterest (N = 10), age (too young; N = 2), or medical illness (N = 2).

Subjects had screening laboratory tests and structural imaging scans (computed tomography [CT] or magnetic resonance imaging [MRI]) to rule out other causes of mental symptoms (e.g., stroke, tumor) and for co-registration with PET scans for region-of-interest (ROI) analyses. One player and two control subjects had CT scans because they could not tolerate MRI (claustrophobia, body metal, body size).

The Mini-Mental State Examination (MMSE), Hamilton Rating Scale for Depression (HAM-D), and a neuropsychological test battery^{8,9} were administered to confirm diagnoses. Clinical assessments were performed within 4 weeks of scanning, and clinicians were blinded to scan results. Informed consent was obtained in accordance with UCLA Human Subjects Protection Committee procedures. Cumulative radiation dosimetry was below the mandated

PET Scanning of Brain Tau in Retired NFL Players

maximum annual dose and in compliance with state and federal regulations.

PET scans were performed using an ECAT HR+ PET or Biograph PET/CT camera (both Siemens/CTI, Knoxville, TN) as detailed previously.^{8,9} In brief, subjects were injected with 10 mCi of FDDNP. FDDNP binding data were quantified using Logan graphical analysis: The slope of the linear portion of the Logan plot is the relative distribution volume (DVR) of the tracer in an ROI divided by that in the reference region (cerebellum). ROIs were traced on co-registered MRI or CT scans for subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, and medial and lateral temporal) regions.^{8,9} Each DVR or binding value was expressed as an average of left and right regions. All scans were read and ROIs drawn by individuals blinded to clinical assessments.

Given the small number of players available for analyses, only non-parametric tests were performed. Controls for comparisons with players were identified using a propensity score matching method, wherein pairs of subjects are matched through a minimum distance estimator that can encompass several covariates.¹² This method thus mitigates potential biases and ensures that controls and players are as similar as possible in other characteristics that can affect FDDNP regional binding levels. FDDNP scans were available for 35 normally aging males from previous studies. We chose age, BMI, years of education, and dementia family history as covariates to match players and controls and used the greedy matching algorithm to identify controls to compare with players. Descriptive statistics were computed for players and controls, and the two-sample Wilcoxon test was used to compare groups on FDDNP binding levels, a global cognitive score (MMSE), and a depression measure (HAM-D). We explored possible relationships between FDDNP binding values and the number of concussions in the players using plots and Spearman correlations in those regions that showed higher signals in players compared with controls.

RESULTS

The players represented a range of positions and diagnoses (linebacker with MCI; quarterback with normal aging; guard with dementia/depression;

defensive lineman with MCI/depression; center with MCI) and played professionally from 10–16 (median, 14) years (Fig. 1). Players and controls were comparable in age (median age for players [controls]: 59 [60]; range: 45–73 [45–66], BMI (players [controls]: 32 [34], 28–42 [28–38]), years of education (players [controls]: 17 [15], 15–18 [13–22]), race (4 white and 1 African American for players and controls) and dementia family history (present in 3 players and 3 controls) (Table 1). Players had significantly higher HAM-D scores (median: 8, range: 5–17) compared with controls (0, 0–3; $p = 0.03$) and a trend towards lower MMSE scores (median: 28, range: 17–30 versus 30, 29–30, $p = .09$) (Table 1).

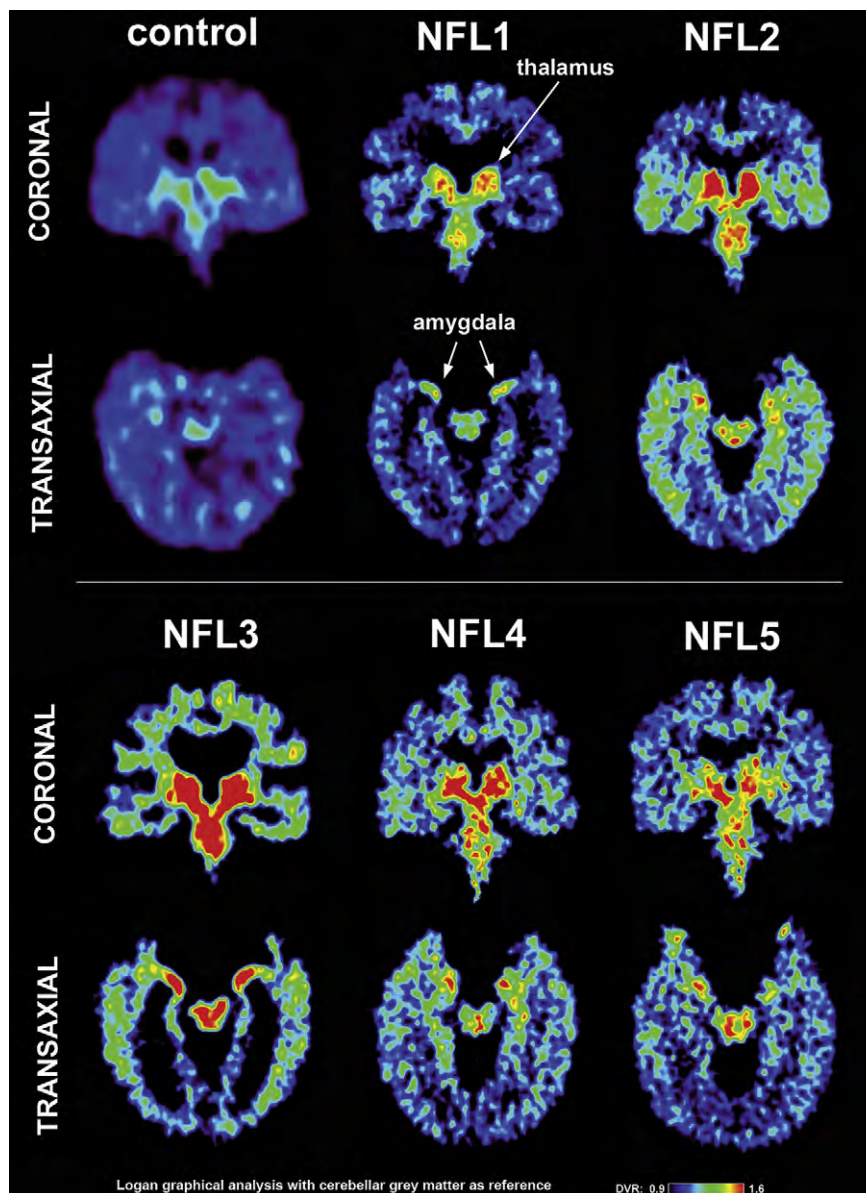
Players had significantly higher FDDNP signals compared with controls in caudate (median levels: 1.48 versus 1.23, $p = 0.03$), putamen (1.47 versus 1.20, $p = 0.05$), thalamus (1.48 versus 1.29, $p = 0.03$), subthalamus (1.45 versus 1.25, $p = 0.03$) midbrain (1.31 versus 1.14, $p = 0.03$), and cerebellar white matter (1.15 versus 1.09, $p = 0.05$) regions. The two groups did not differ significantly in FDDNP binding in cortical regions except for the amygdala (1.30 versus 1.14, $p = 0.03$) (Table 1; Figs. 1, 2).

Plots of FDDNP binding values versus number of concussions in regions that showed higher signals in players compared with controls are presented in Figure 3. Although none of the Spearman correlations reached statistical significance (as expected due to the small sample size), the plots show an increase in FDDNP binding levels with increase in number of concussions.

DISCUSSION

These initial FDDNP-PET findings in retired NFL players with histories of cognitive and mood symptoms demonstrate high signals in the amygdala and subcortical regions compared with controls. Although the subject groups were matched for important variables, such as age, BMI, and educational achievement, these preliminary results need interpretation with caution given the small sample size and multiple uncorrected statistical comparisons. Also, not all subjects had MRI scans for co-registration with PET, which could influence ROI values, although comparable numbers of players and controls had MRI scans (4 and 3, respectively). Other factors that could influence the results would be differences in cerebrovascular health and genetic risk between players and

FIGURE 1. FDDNP-PET scan results for NFL players and a control. Coronal and transaxial FDDNP-PET scans of the retired NFL players include:
 NFL1: 59-year-old linebacker with MCI, who experienced momentary loss of consciousness after each of two concussions;
 NFL2: 64-year-old quarterback with age-consistent memory impairment, who experienced momentary loss of consciousness and 24-hour amnesia following one concussion;
 NFL3: 73-year-old guard with dementia and depression, who suffered brief loss of consciousness after 20 concussions, and a 12-hour coma following 1 concussion;
 NFL4: 50-year-old defensive lineman with MCI and depression, who suffered two concussions and loss consciousness for 10 minutes following one of them;
 NFL5: 45-year-old center with MCI, who suffered 10 concussions and complained of light sensitivity, irritability, and decreased concentration after the last two.
 The players' scans show consistently high signals in the amygdala and subcortical regions and a range of cortical binding from extensive to limited, whereas the control subject shows limited binding in these regions. Red and yellow areas indicate high FDDNP binding signals.



*PET Scanning of Brain Tau in Retired NFL Players***TABLE 1. Subject Characteristics and Regional FDDNP Binding Values**

Characteristic ^a	Players (N = 5)	Controls (N = 5)
Age—yr	59 (45–73)	60 (45–66)
Education—yr	17 (15–18)	15 (13–22)
AD family history—none (%)	3 (60)	3 (60)
Body Mass Index	32 (29–42)	34 (28–38)
Mini Mental State Exam	28 (17–30)	30 (29–30)
HAM-D ^b	8 (5–17)	0 (0–3)
FDDNP binding values^c		
Amygdala	1.30 (1.27–1.45)	1.14 (1.09–1.17)
Caudate	1.48 (1.46–1.81)	1.23 (1.16–1.34)
Putamen	1.47 (1.35–1.60)	1.20 (1.14–1.35)
Thalamus	1.48 (1.41–1.54)	1.29 (1.07–1.39)
Subthalamic	1.45 (1.31–1.51)	1.25 (1.09–1.30)
Midbrain	1.31 (1.27–1.39)	1.14 (1.10–1.18)
Cerebral white matter	1.15 (1.12–1.27)	1.09 (1.08–1.12)
Frontal	1.12 (0.97–1.16)	1.03 (0.98–1.13)
Parietal	1.05 (0.96–1.12)	1.04 (0.98–1.07)
Medial temporal	1.15 (1.07–1.19)	1.12 (1.08–1.18)
Lateral temporal	1.09 (1.00–1.13)	1.08 (1.03–1.13)
Posterior cingulate	1.08 (1.00–1.17)	1.09 (1.05–1.11)

Notes: ^aData are presented as median (range) unless specified otherwise.

^bHamilton Rating Scale for Depression-21 item version; groups were significantly different: Wilcoxon statistic $U = 15$, $p = 0.03$.

^cSignificant differences between groups in the following regions: amygdala: $U = 15$, $p = 0.03$; caudate: $U = 15$, $p = 0.03$; putamen: $U = 16$, $p = 0.05$; thalamus: $U = 15$, $p = 0.03$; subthalamic: $U = 15$, $p = 0.03$; midbrain: $U = 15$, $p = 0.03$; cerebellar white matter: $U = 16$, $p = 0.04$.

controls. Despite such limitations, these elevated amygdala and subcortical FDDNP binding patterns in players are consistent with the fibrillary tau deposition patterns observed at autopsy in CTE cases.⁵ Only patchy cortical tau deposits have been reported in mild CTE cases, except for the amygdala, where they are dense.⁴

The pattern of higher FDDNP binding values in players with a greater number of concussions (Fig. 3) suggests a link between the players' history of head injury and FDDNP binding. Moreover, these binding patterns (high subcortical and low cortical binding except for the amygdala) are consistent with tau deposition patterns observed in autopsy studies of CTE⁵ and differ from those observed in patients with cognitive and mood symptoms without prior head trauma, who mainly present with increased cortical FDDNP binding. In patients with geriatric depression, FDDNP binding is highest in the posterior cingulate and lateral temporal regions,¹⁴ whereas patients with Alzheimer dementia show high binding values throughout the cortex

(parietal, medial and lateral temporal, frontal and posterior cingulate regions).^{7–9} In patients with MCI, FDDNP binding is high in medial temporal, frontal, and parietal regions.⁸

FDDNP binds to both fibrillary tau and amyloid, but neuropathological studies indicate that amyloid plaques (mostly diffuse cortical) are observed in less than a third of CTE cases in retired football players.^{5,13} This suggests that a high proportion of the FDDNP signal in the players represents fibrillary tau deposition. Using a tau marker for detection and tracking of neurodegenerative disease is critically important because severity of tau load, rather than amyloid burden, correlates with rates of neuronal loss.⁹ To date, FDDNP is the only available imaging probe that provides in vivo measures of tau in humans.

Players had greater depressive symptoms than controls, as well as evidence of cognitive impairment (3 MCI, 1 dementia). Elevated FDDNP binding is associated with depressive symptoms in normal aging¹⁴ and geriatric depression,¹⁵ and with cognitive symptoms in normal aging, MCI, and dementia.^{8,9} Thus, these increased FDDNP signals appear to reflect a range of mental symptoms that have been observed in CTE cases.

Despite the devastating consequences of mild TBI from contact sports and military exposure to explosive blasts and the large group of those exposed, the syndrome has only recently received heightened attention. Specific treatments have not been developed, and no method for early detection has yet been established. Early recognition and identification of those at high risk would allow clinicians to develop strategies and interventions to protect those with early symptoms rather than attempt to repair damage once it becomes extensive.

Previous studies in patients with MCI show that FDDNP-PET patterns may predict future cognitive decline and development of dementia.⁹ Large-scale longitudinal studies are necessary to determine the utility of detecting tau pathology in head trauma victims who are not yet experiencing mood or cognitive symptoms and whether this technology will facilitate development of prevention strategies. Further, the added health benefits of FDDNP scanning on a large scale remains to be addressed. Previous analysis, however, indicates that appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up,

FIGURE 2. Scatter plots of FDDNP binding values in players and controls. FDDNP binding scatter plots for the 5 players (red circles) and 5 controls (blue circles) in the amygdala, midbrain, thalamus, and caudate regions illustrate the significantly higher values in players compared with controls. FDDNP binding is expressed in terms of the DVR derived by the Logan graphic method, with the cerebellum as the reference region.

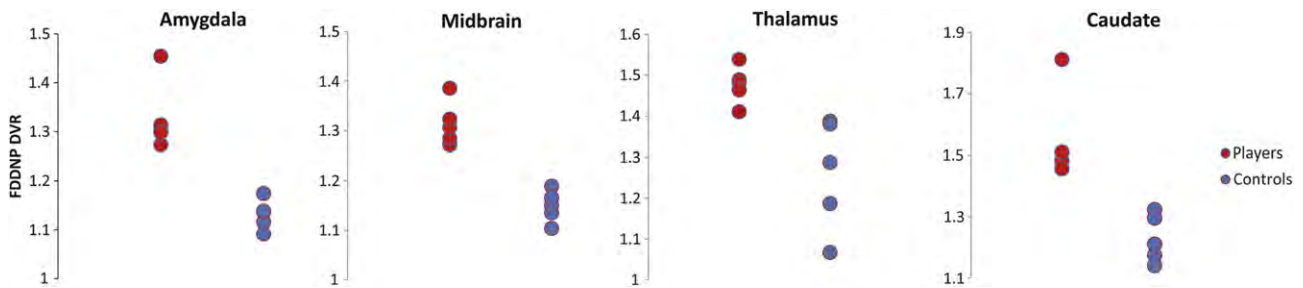
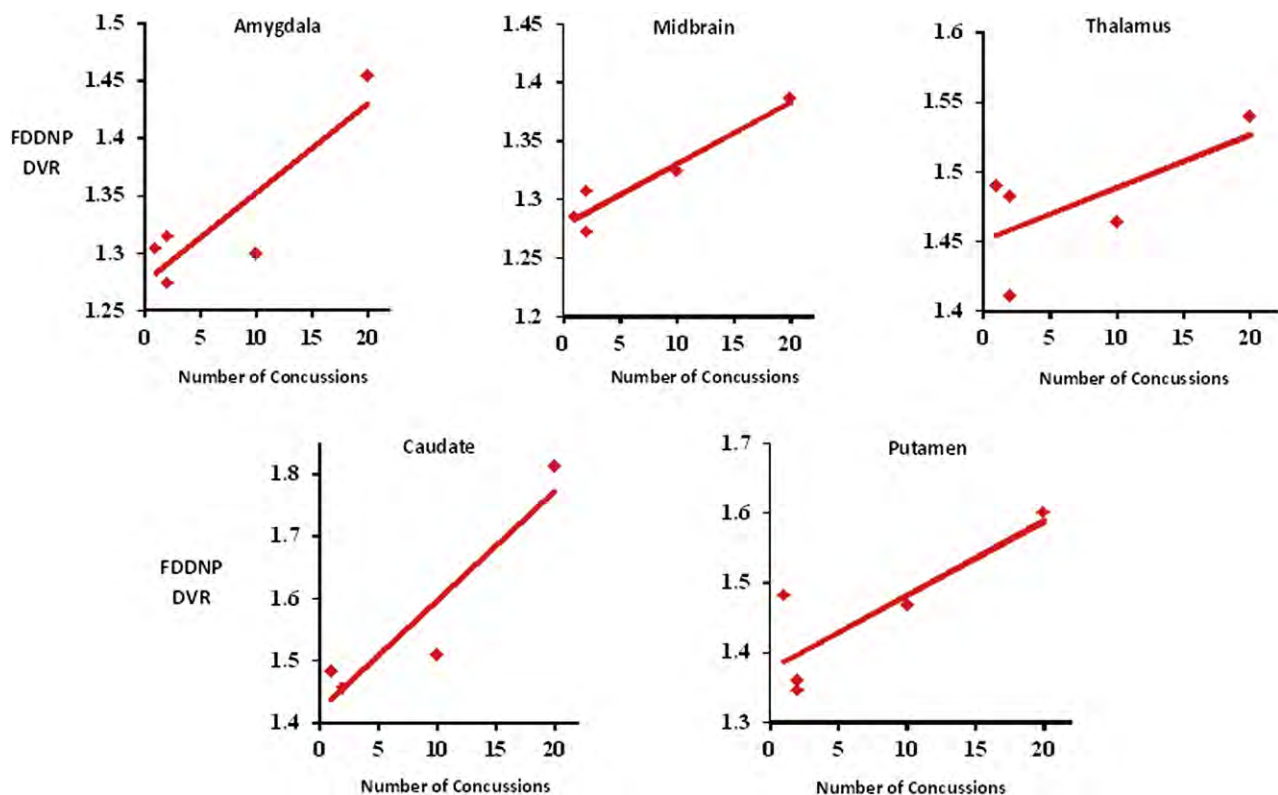


FIGURE 3. FDDNP binding levels versus number of concussions in retired players. Examination of plots showing FDDNP DVR binding values according to number of concussions in retired players suggests an association between a greater number of concussions and higher binding in regions that were found to show significantly higher FDDNP binding in players compared with controls. FDDNP binding is expressed in terms of the DVR derived by the Logan graphic method, with the cerebellum as the reference region.



without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure.¹⁶

These findings suggest that FDDNP-PET could facilitate early recognition and intervention of trauma-related neurodegeneration through premorbid detection. Providing a non-invasive means of early

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detection is a critical first step to developing interventions to prevent symptom onset and progression. Direct and indirect costs of TBI totaled an estimated \$77 billion in the United States in 2000.¹⁷ Given the large number of people at risk—not just athletes but military personnel, auto accident victims, and others—the potential public health impact is considerable.

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The University of California, Los Angeles, owns a U.S. patent (6,274,119) entitled "Methods for Labeling β -Amyloid Plaques and Neurofibrillary Tangles," that uses the approach outlined in this article. Drs. Small and Barrio are among the inventors, have received royalties, and may receive royalties on future sales. Dr. Small reports having served as a consultant and/or having received lecture fees from Janssen, Lilly, Novartis, and Pfizer. Dr. Barrio reports having served as a consultant and having received lecture fees from Nihon Medi-Physics Co, Bristol-Meyer Squibb, PETNet Pharmaceuticals, and Siemens. Drs. Ercoli, Kepe, Siddarth, Merrill, Bookheimer, Omalu, and Bailes and Ms. Donoghue and Ms. Martinez have no financial conflicts of interest.

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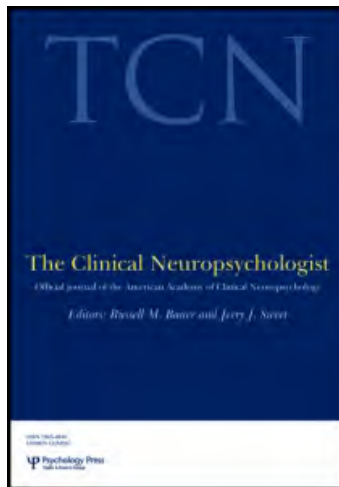
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An Integrated Review of Recovery after Mild Traumatic Brain Injury (MTBI): Implications for Clinical Management

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AN INTEGRATED REVIEW OF RECOVERY AFTER MILD TRAUMATIC BRAIN INJURY (MTBI): IMPLICATIONS FOR CLINICAL MANAGEMENT

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The diagnosis and treatment of mild traumatic brain injury (MTBI) have historically been hampered by an incomplete base of scientific evidence to guide clinicians. One question has been most elusive to clinicians and researchers alike: What is the true natural history of MTBI? Fortunately, the science of MTBI has advanced more in the last decade than in the previous 50 years, and now reaches a maturity point at which the science can drive an evidence-based approach to clinical management. In particular, technological advances in functional neuroimaging have created a powerful bridge between the clinical and basic science of MTBI in humans. Collectively, findings from clinical, basic science, and functional neuroimaging studies now establish a foundation on which to build integrative theories and testable hypotheses around a comprehensive model of MTBI recovery. We review the current scientific literature on postconcussion symptom recovery, neuropsychological outcome, and neurophysiological healing after MTBI. Special emphasis is placed on how the new evidence base can help guide clinicians in the evaluation and management of military-related MTBI.

Keywords: Brain injury; Concussion; Neuropsychological tests; Military medicine.

INTRODUCTION

Mild traumatic brain injury (MTBI) has long been considered one of the most challenging encounters for even the most skilled neuropsychologists and other

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clinicians throughout the neurosciences. The diagnosis of MTBI historically has been hampered by a lack of consensus around the essential, defining characteristics of injury and the limited utility of traditional methods—e.g., Glasgow Coma Scale (Teasdale & Jennett, 1974)—for detecting and classifying less severe grades of acquired brain injury (Iverson, Lange, Gaetz, & Zasler, 2007a). More recently, attempts at multidimensional definitions that incorporate information on biomechanics, acute injury characteristics, and clinical course assist clinicians in making the most accurate *diagnosis* of MTBI (Holm, Cassidy, Carroll, & Borg, 2005; Kay et al., 1993).

There remains great debate, however, about the expected recovery course after MTBI. Historically, science has not provided a sound evidence base to answer the question: *What is the true natural history of MTBI?* Thankfully, many recent breakthroughs have advanced our understanding of the biomechanics, neurophysiology, clinical presentation, and expected recovery course associated with MTBI (see reviews in Iverson et al., 2007a; McCrea, 2007). Collectively, this body of work moves us closer to a more complete understanding of the true natural history of MTBI, which also translates directly to evidence-based methods for clinical evaluation, management, and enhanced outcome.

Interestingly, the sports medicine world has been the platform for many recent advances in the science of MTBI through the prospective study of sport-related concussion. More than 20 years ago, Barth, Macciocchi, and colleagues recognized that many aspects inherent to sport-related concussion essentially create a laboratory for the study of MTBI (Barth et al., 1989; Macciocchi, Barth, Alves, Rimel, & Jane, 1996). Applying the methodological advantages first identified in Barth's Sports as a Laboratory Assessment Model (SLAM; Barth, Freeman, Broshek, & Varney, 2001; Barth, Freeman, & Winters, 2000), several studies of sport-related concussion have since not only assisted clinicians in sports medicine with respect to clinical decision making about eventual return to competition and preventing the risks of repeat injury, but also informed the broader neurosciences with new evidence on the basic and clinical science of MTBI (Belanger & Vanderploeg, 2005; Collins, Iverson, Gaetz, & Lovell, 2007; Guskiewicz et al., 2003; McCrea et al., 2003; Moser et al., 2007).

Clinicians in our armed forces now face a new set of challenges in the evaluation and management of MTBI encountered by military personnel serving in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) (Hoge et al., 2008; McCrea et al., 2008). Traumatic brain injury (TBI) has been referred to as the "signature injury" among United States military personnel involved in combat in Iraq and Afghanistan, although precise estimates of TBI incidence among U.S. military personnel have been difficult to pin down (Iverson, Langlois, McCrea, & James, 2009 this issue). Regardless of the true epidemiology, we know from direct accounts of clinicians that all echelons of care are frequently called upon to triage and manage traumatic brain injury at all severity levels, with the overwhelming majority falling into the MTBI classification. Much like managing sport-related concussion, these clinicians are called upon to make rapid, informed determinations about injury severity, level of recovery, and a warrior's fitness to return to active duty following MTBI. Measures to protect military personnel from the potentially negative or catastrophic risks associated with recurrent MTBI are also relevant in this setting.

This article is intended to summarize the relatively new evidence base that advances our scientific understanding of the true natural history of MTBI. We will specifically focus on what the scientific evidence base now tells us about the expected course of recovery in postconcussion symptoms, cognition, and neurophysiology following MTBI, ultimately integrating this information into a theoretical, comprehensive model of MTBI recovery. In keeping with the theme set forth in the series of papers stemming from the International Conference on Behavioral Health and Traumatic Brain Injury, special emphasis will be placed on how the scientific evidence base may help guide clinicians in the evaluation and management of military-related MTBI.

CLINICAL RECOVERY AFTER MTBI

Symptom recovery

In 2004 The World Health Organization (WHO) Collaborating Centre Task Force on Mild Traumatic Brain Injury published a detailed review of the literature on prognosis after MTBI. In total, 120 studies that comprised what the task force considered to be the best-evidence synthesis on prognosis after MTBI met criteria for inclusion in its critical review (Carroll et al., 2004). The WHO task force summarized the results of several studies on self-reported symptoms after MTBI, indicating that headache, blurred vision, dizziness, sleep problems, subjective memory problems, and other cognitive difficulties are the most commonly experienced symptoms after MTBI (Bazarian et al., 1999; Cline & Whitley, 1988; Garraway & Macleod, 1995; Lidvall, Linderoth, & Norlin, 1974a, 1974b; Lowdon, Briggs, & Cockin, 1989; Macciocchi et al., 1996; P. R. McCrory, Ariens, & Berkovic, 2000; Paniak, Phillips, Toller-Lobe, Durand, & Nagy, 1999; Paniak et al., 2002; Riemann & Guskiewicz, 2002). The WHO's extensive review indicated that, in both children and adults, symptoms after MTBI are typically temporary and self-limiting in nature, with resolution within days to weeks post-injury in an overwhelming majority of MTBI patients (Carroll et al., 2004). The WHO task force concluded, based on its review, that there was consistent and methodologically sound evidence that prognosis after MTBI is highly favorable, with gradual resolution of symptoms and little evidence of residual cognitive, behavioral or academic deficits (Carroll et al., 2004).

Researchers have capitalized on the methodological advantages of Barth's SLAM approach (Barth et al., 2001, 2000) to prospectively *measure* the scope and severity of symptoms beginning within minutes of injury, and plotted the time course of symptom recovery over the ensuing hours, days, and weeks (Belanger & Vanderploeg, 2005; Lovell et al., 2003; McCrea et al., 2003). These studies indicate a pattern of gradual symptom recovery within the first 1 to 2 weeks after MTBI in the overwhelming majority of cases, extending out to several weeks in some instances. Figure 1 provides results from a prospective study on the effects of sport-related concussion in a large sample of college athletes, illustrating the course of symptom recovery from time of injury to 90 days post-injury (McCrea et al., 2003). This recovery curve illustrates that: (a) symptomatology is most severe immediately following injury, (b) a pattern of symptom recovery is evident within the first

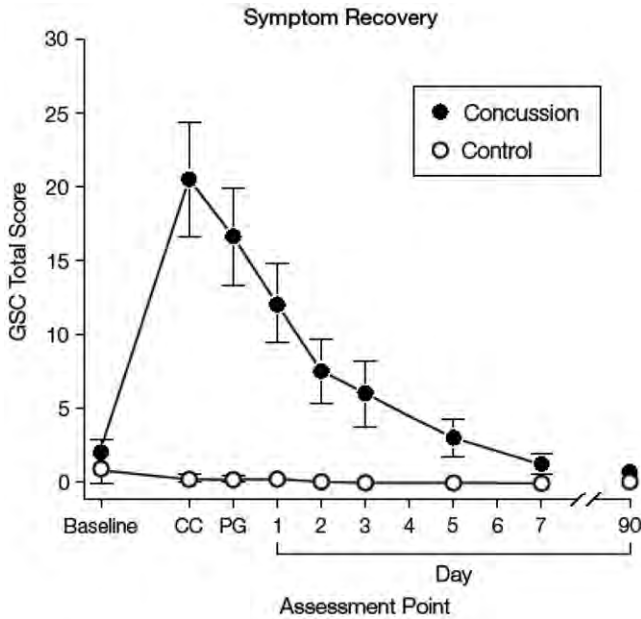


Figure 1 Symptom recovery following MTBI in college football players. GSC=Graded Symptom Checklist. Higher scores on the GSC indicate more severe symptoms; error bars indicate 95% confidence intervals; baseline is pre-injury; CC indicates time of concussion; PG, post-game/post-practice. Figure from McCrea et al., 2003.

2 hours of concussion, and (c) the pattern of symptom recovery continues on a gradual course over the first several days. There is no significant difference between the symptom scores for injured people and normal controls by day seven post-injury. Moreover, delayed onset of symptoms is a relatively rare occurrence.

Contrary to previous reports (Alexander, 1995; McLean, Temkin, Dikmen, & Wyler, 1983), a very small percentage of civilian trauma cases report symptoms 12 months after MTBI in prospective studies (Alves, Macciocchi, & Barth, 1993; Iverson, 2005). For milder injuries, such as those observed in sports, only a small percentage of cases report symptoms beyond 30 days post-injury. For example, Figure 2 categorizes the rate of symptom recovery by 635 high school and college athletes following sport-related concussion. Overall, more than 85% of injured participants reported a full symptom recovery in less than 1 week, including 21% who reportedly recovered within the first day. Fewer than 3% of participants reported symptoms beyond 1 month post injury, which is considerably lower than previous reports of persistent post-concussion syndrome incidence rates in the order of 15% (Alexander, 1995; McLean et al., 1983), but consistent with conclusions of the WHO task force.

In the case of uncomplicated MTBI with no structural injury visualized on neuroimaging, the WHO task force summarized the literature on MTBI symptom recovery by stating that there is evidence that persistent symptoms beyond the typical recovery period of several days to weeks may be attributable to factors other than MTBI (Carroll et al., 2004). Demographic (e.g., female gender,

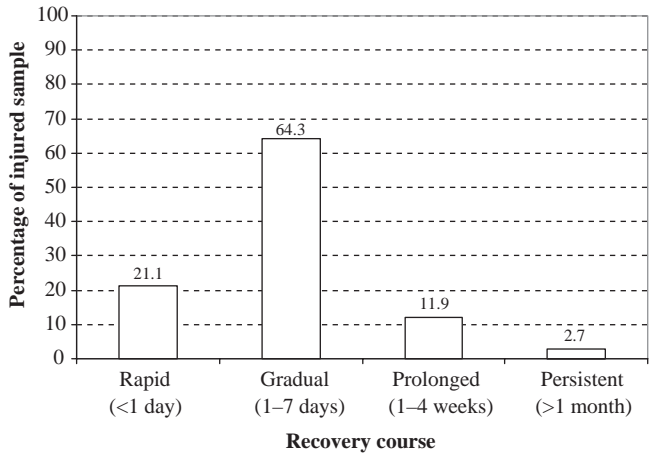


Figure 2 Distribution of post-injury symptom recovery course in 635 concussed high school and college athletes. The percentage of the injured sample recovered at each interval is based on clinical documentation from physicians and certified athletic trainers on duration of symptoms.

older age), psychosocial (e.g., unstable relationships, lack of social support system, pre-existing psychiatric problems or personality disorder, substance abuse or dependence), medical (e.g., severe associated injuries, comorbid medical or neurologic disorders, prior history of MTBI) and situational (e.g., litigation/compensation, concurrent post-traumatic stress disorder [PTSD]) factors have been implicated as predictors of prolonged symptoms after MTBI (Carroll et al., 2004; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006). In more severe forms of complicated MTBI, focal, structural damage detected on head CT or brain MRI may increase the risk of slower recovery with prolonged symptoms and poorer overall outcome more consistent with that seen in moderately severe TBI (Borgaro, Prigatano, Kwasnica, & Rexer, 2003; Iverson, 2006; Kurca, Sivak, & Kucera, 2006; Williams, Levin, & Eisenberg, 1990).

Neuropsychological recovery

In our review of neuropsychological recovery after MTBI, we benefit from the combined work of prominent MTBI researchers more than a decade ago and a number of meta-analytic studies that in the last 3 years have provided a comprehensive summary of the scientific literature.

Seminal work from more than a decade ago first began to characterize neuropsychological recovery after MTBI. Dikmen and colleagues reported on what at the time was the largest prospective study of TBI patients, including a cohort of 161 MTBI patients (Dikmen, Machamer, Winn, & Temkin, 1995). Their results showed that the magnitude and pervasiveness of impairments in cognitive functioning 1 year after injury was highly dependent on TBI severity. In the MTBI sample neuropsychological performance was comparable to trauma controls 1 year post-injury, with no significant differences between the MTBI and control groups. Dikmen and colleagues concluded that their findings were consistent with

other studies from that era (Dikmen, McLean, & Temkin, 1986; Levin et al., 1987) indicating that MTBI was not associated with long-term persistent neuropsychological impairments.

Separate meta-analytic studies by Larrabee (1997) and Binder, Rohling and Larrabee (1997b) later showed very small effect sizes (e.g., d statistic in the range of 0.10 to 0.20) when considering the overall neuropsychological effects of MTBI, ultimately concluding that meta-analytic data from well-conducted studies showed good long-term neuropsychological recovery for most persons after MTBI.

Several more recent meta-analytic studies have either replicated or advanced the science of neuropsychological recovery after MTBI. In 2003, Schretlen and Shapiro (2003) published a review of the effects of traumatic brain injury on cognitive functioning. This paper was a unique contribution to the literature by way of its quantitative review of cognitive functioning across the *spectrum* of TBI severity. They conducted a meta-analysis of 39 mostly cross-sectional studies of the cognitive effects of MTBI and moderate-severe TBI from the acute phase through long-term follow-up. These studies reported 48 comparisons of TBI patients ($N=1,716$) and control participants ($N=1,164$). Averaged across all follow-up periods, the effect of moderate-severe TBI (weighted mean Cohen's $d=-0.74$) was more than three times the effect of MTBI (weighted mean $d=-0.24$) on overall cognitive functioning. For MTBI, the initial weighted d of -0.41 was moderate, but the overall cognitive test performance by MTBI patients was essentially indistinguishable from that of matched controls by 1 month post-injury ($d=-0.08$). Schretlen and Shapiro concluded that overall cognitive functioning recovers most rapidly during the first few weeks following MTBI, and essentially returns to baseline within 1 to 3 months.

Belanger and colleagues (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005) published a review on factors moderating neuropsychological outcome following MTBI. They conducted a meta-analysis based on 39 studies involving 1463 MTBI patients and 1191 controls. The overall effect of MTBI on neuropsychological functioning was moderate ($d=0.54$). However, findings were moderated by cognitive domain, time since injury, patient characteristics, and sampling methods. In unselected or prospective samples the overall analysis revealed no residual neuropsychological impairments by 90 days post-injury ($d=0.04$). In contrast, clinic-based samples and samples including participants in litigation were associated with greater cognitive sequelae of MTBI ($d=0.74$ and 0.78 , respectively at 3 months or greater). Litigation was actually associated with stable or worsening cognitive functioning over time. Belanger and colleagues (2005) concluded that MTBI had little to no effect on neuropsychological functioning by 3 months or greater post-injury in a MTBI population. This study also highlighted the point that sampling method (i.e., clinic-based versus unselected samples) is paramount when studying neuropsychological outcome after MTBI.

Frencham, Fox, and Maybery (2005) also conducted a meta-analytic review of neuropsychological studies of MTBI published since the previous meta-analysis by Binder and colleagues (Binder, 1997; Binder & Rohling, 1996; Binder, Rohling, & Larrabee, 1997a). Their meta-analysis revealed 17 studies that were suitable for inclusion, from which effect sizes on neuropsychological effects were aggregated. The overall effect size was $G=0.32$, but post-acute effect sizes were very

small ($G=0.11$). Similar to the findings of other researchers, Frencham and colleagues concluded that time since injury was found to be the most significant moderator of neuropsychological outcome after MTBI, with effect sizes approaching zero further out from MTBI.

Iverson (2005) took an innovative approach to studying the neuropsychological effects of MTBI by converting effect sizes from previous meta-analytic studies to a standard metric (i.e., the metric used for IQ scores with a mean of 100 and standard deviation of 15). This exercise illustrated that moderate and severe brain injuries have a pronounced negative effect on cognitive functioning, but MTBI has essentially no measurable effect on cognitive functioning after the acute recovery period using a metric (i.e., IQ scores) more easily understood by clinicians. Iverson also compared the overall cognitive effects of MTBI with other conditions based on a quantitative summary of hundreds of studies and thousands of patients. This approach also revealed that the effects of MTBI on cognition and memory after the acute recovery period are very small, considerably smaller than the effects of depression, bipolar disorder, ADHD, benzodiazepine use/withdrawal, litigation, and malingering (see Figure 3).

As in the general MTBI literature, studies of sport-related concussion have also revealed a rapid return to normal neuropsychological functioning in the first 2 weeks post-injury, with very small neuropsychological effect sizes further out from concussion. A 2005 meta-analysis by Belanger and Vanderploeg (2005) was conducted to determine the impact of sport-related concussion on cognitive functioning. Their analyses were based on 21 studies involving 790 cases of concussion and 2014 controls. The overall effect of concussion ($d=0.49$) was comparable to the effect sizes cited in prior meta-analyses of the civilian trauma MTBI population, including results from the earlier meta-analysis by the same researchers which reported an overall effect size of $d=0.54$ (Belanger et al., 2005). Belanger and Vanderploeg (2005) concluded that their meta-analysis provided compelling evidence that sport-related concussion results in no significant effect on neuropsychological functioning by 7–10 days post-injury in the athletic population at large. In tandem with their concurrent meta-analysis in civilian trauma cases (Belanger et al., 2005), this study also suggested a similar course and outcome following sport-related and non-sport related MTBI, which lends further support to the methodological advantages of the SLAM model to study MTBI in general.

In summary, several meta-analyses and prospective studies over the past decade indicate that MTBI is most often followed by a favorable course of neuropsychological recovery over a period of days to weeks, with little or no indication of permanent impairment on neuropsychological testing by 3 months post-injury in group studies. It should be acknowledged that meta-analyses represent an aggregation of effect sizes derived from multiple groups across multiple studies, but can obscure small subgroup or individual effects (Iverson, Brooks, Collins, & Lovell, 2006). Complicated MTBI characterized by structural brain damage visualized on acute neuroimaging may increase the risk for slow or incomplete recovery after MTBI, making predictions of outcome considerably less precise in this group (Borgaro et al., 2003; Iverson, 2006; Kurca et al., 2006; Williams et al., 1990).

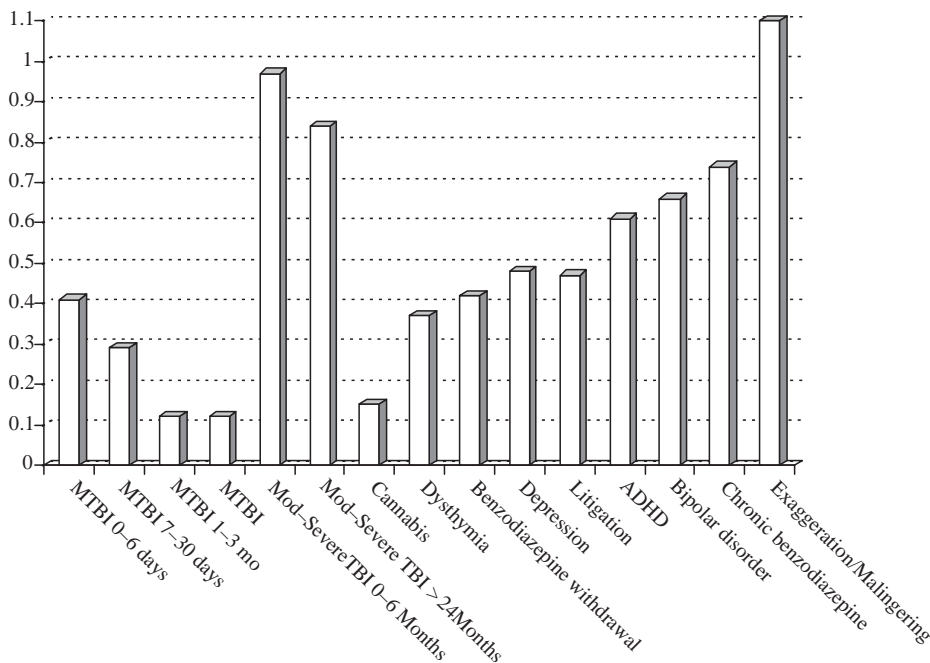


Figure 3 Effect sizes of MTBI on overall neuropsychological functioning. Effect sizes typically are expressed in pooled, weighted standard deviation units. However, across studies there are some minor variations in the methods of calculation. By convention, effect sizes of .2 are considered small, .5 medium, and .8 large. This is from a statistical, not necessarily clinical, perspective. In this figure the overall effect on cognitive or neuropsychological functioning is reported. Effect sizes less than .3 should be considered very small and difficult to detect in individual patients because the patient and control groups largely overlap. MTBI: 0–6 days, 7–30 days, 1–3 months, moderate-severe TBI 0–6 months, >24 months (all in Schretlen & Shapiro, 2003), 39 studies, $N=1716$ TBI, $N=1164$ controls; MTBI (Binder et al., 1997a), 11 studies, $N=314$ MTBI, $N=308$ controls. Cannabis (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003): long-term regular use, 11 studies, $N=623$ users, $N=409$ non or minimal users. Dysthymia, depression, & bipolar disorder (Christensen, Griffiths, Mackinnon, & Jacomb, 1997): 3 comparisons for dysthymia, 97 comparisons for depression, and 15 comparisons for bipolar disorder. Benzodiazepine withdrawal (Barker, Greenwood, Jackson, & Crowe, 2004b): 10 studies, long-term follow-up, 44 comparisons. Litigation/financial incentives (Binder & Rohling, 1996): 17 studies, $N=2,353$ total. ADHD (Frazier, Demaree, & Youngstrom, 2004): based on Full Scale IQ, 123 studies. Chronic benzodiazepine use (Barker, Greenwood, Jackson, & Crowe, 2004a): 13 studies, $N=384$, 61 comparisons. Exaggeration/malingering (Vickery, Berry, Inman, Harris, & Orey, 2001): 32 studies published between 1985 and 1998, 41 independent comparisons. Reference: Iverson, 2005. Figure reproduced with kind permission from G. L. Iverson, Outcome from mild traumatic brain injury, *Current Opinion in Psychiatry*, 18 p. 306 © 2005, Wolters Kluwer Health. Lippincott Williams & Wilkins.

NEUROPHYSIOLOGICAL RECOVERY AFTER MTBI

Pathophysiology of MTBI

The “mild” classification range is extraordinarily broad from the perspective of pathophysiology and neurobiology. Most classification systems used by researchers and clinicians include injuries that are so mild that symptomatic

recovery can occur within the same day. The person might simply have felt dazed for a brief period of time. Some degree of headache, dizziness, and cognitive slowing might have been present for a couple hours but then resolved. Thus, the person experienced a blow to the head that affected cellular physiology temporarily, with rapid return to asymptomatic status.

The other end of the mild spectrum abuts the moderate TBI classification range. These injuries can be characterized by loss of consciousness in excess of 10 minutes and many hours of post-traumatic amnesia. These injuries can be associated with macroscopic evidence of brain damage, such as a contusion visible on CT (i.e., the so-called “complicated” MTBI). Macroscopic abnormalities within brain tissue or outside the brain (i.e., extra-axial space) can be identified using neuroimaging (e.g., CT or MRI). In the most severe form of MTBI, these macroscopic injuries can include hemorrhagic contusions, non-hemorrhagic contusions, hemorrhagic or non-hemorrhagic shearing injuries, and cerebral edema evidenced on structural neuroimaging. Extra-axial manifestations of injury can include epidural hematomas, subdural hematomas, subarachnoid hemorrhage, and intraventricular hemorrhage. This represents a small percentage of MTBIs, and some clinicians and researchers are comfortable conceptualizing these injuries as “moderate.”

Injuries that fall on the mild end of the MTBI spectrum (“uncomplicated” concussion with brief or no amnesia or unconsciousness) are likely associated with low levels of axonal stretching, which result in only temporary changes in neurophysiology. Giza and Hovda (2001) describe a model, conceptualized as a multilayered neurometabolic cascade, for the complex interwoven cellular and vascular changes that occur following concussive forces applied to the brain (see Figure 4). The neurobiology involves ionic shifts, abnormal energy metabolism, diminished cerebral blood flow, and impaired neurotransmission. Fortunately, for the vast majority of affected cells, there appears to be a reversible series of neurometabolic events (Giza & Hovda, 2001; Iverson, 2005; Iverson et al., 2007a)

The ultimate fate of neurons relates to the extent of traumatic axonal injury, which can culminate in secondary axotomy (see Buki & Povlishock, 2006, for a review). High intracellular Ca^{2+} levels, combined with stretch injury, can initiate an irreversible process of destruction of microtubules within axons. The disruption of the microtubular and neurofilament components contributes to axonal swelling and detachment (i.e., secondary axotomy). Some, but not all, cells that experience secondary axotomy will degenerate and die through necrotic or apoptotic mechanisms.

In general, however, most injured cells (a) do not undergo secondary axotomy and (b) appear to recover normal cellular function. In other words, for most individuals who sustain an MTBI, it appears that the brain undergoes dynamic restoration and, in due course, individuals return to a normal state of neuronal functioning (Iverson, 2005; Iverson et al., 2007a).

Influence of activity on acute physiology

When a warrior, civilian, or athlete sustains an MTBI, a decision must be made regarding return to duty, work, or play. It is widely accepted in amateur

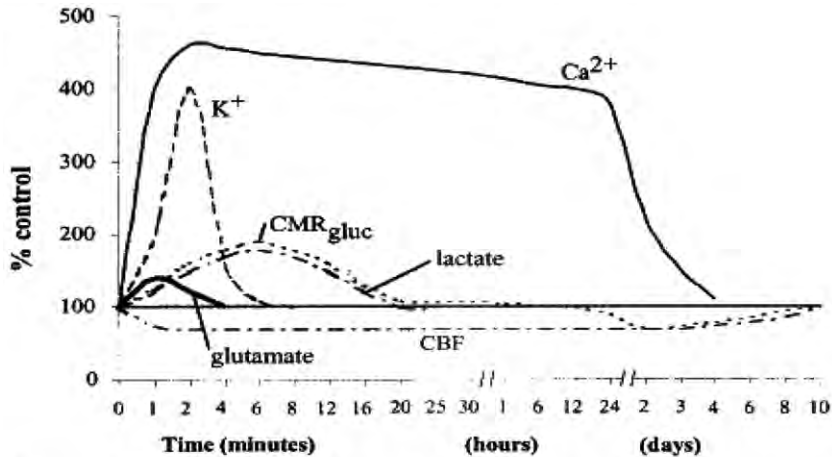


Figure 1. Neurometabolic cascade following experimental concussion. K^+ , potassium; Ca^{2+} , calcium; CMRgluc, oxidative glucose metabolism; CBF, cerebral blood flow. (Reprinted with permission. Giza CC, Hovda DA. Ionic and metabolic consequences of concussion. In: Cantu RC, Cantu RI. *Neurologic Athletic and Spine Injuries*. St Louis, MO: WB Saunders Co; 2000:80–100.).

Figure 4 Neurometabolic cascade following experimental concussion in rats. Reference: Giza and Hovda, 2001 (Reprinted with permission).

athletics that athletes who sustain a concussion should not return to the practice or game in which they were injured. The now widely cited recommendation is that athletes should rest until they are asymptomatic. In general, rest means no vigorous physical activity or heavy mental exertion. From a practical perspective, this often means taking a few days off duty, work, or school.

When the athlete is asymptomatic, a return to light aerobic exercise is recommended as described in the two agreement statements following the International Concussion in Sport Conferences in Vienna (Aubry et al., 2002) and Prague (P. McCrory et al., 2005). The protocol, which is based mostly on expert consensus without empirical data, involves an athlete moving through the following exertional steps in 24-hour periods: (a) light aerobic exercise (e.g., walking or a stationary biking), (b) sport-specific training (e.g., ice skating in hockey or running in soccer), and (3) non-contact training drills (usually heavily exertional). Athletes then progress to contact or full return to play. If the athlete's previously resolved post-concussion symptoms return at any step, the athlete should return to the previous exertion level at which they were last asymptomatic.

What is less clear is whether exercising too soon can have short-, medium-, or long-term adverse effects on an injured athlete, warrior, or civilian. This, of course, is very difficult to study. Theoretically, if the brain is (a) in a state of neurometabolic crisis, and (b) using resources to try to adapt to, modify, and re-regulate, then (c) exertion, such as exercise, could worsen the neurometabolic crisis and delay recovery. Most research designs addressing these issues cannot be implemented with humans. Thus, most of the work in this area has been done with animals.

A series of interesting studies relating to exercise following MTBI have been conducted by Griesbach and colleagues. In one study, 18 rats were injured using a fluid percussion device and then they were returned to cages with or without running wheels (Griesbach, Gomez-Pinilla, & Hovda, 2004a). After a few days they were sacrificed and molecular markers of plasticity, such as Brain-Derived Neurotrophic Factor (BDNF) and Synapsin I were examined. BDNF helps regulate neuronal growth, helps with neuronal survival after injury, and facilitates synaptic function. Synapsin I is involved in synaptic vesicle clustering and release. There was an increase in molecular markers of plasticity measured at 7 days post-injury. However, if injury was followed by acute voluntary exercise, these same molecular markers were decreased. In this study early physiological stimulation through voluntary exercise reduced the capacity for plasticity in the injured rat brain.

In a larger study, Griesbach and colleagues (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004b) administered fluid percussion brain injuries to 161 rats (mean duration of loss of consciousness = 82 seconds, $SD = 54$ seconds; mean duration of apnea = 14 seconds, $SD = 11$ seconds). Some rats were allowed to exercise immediately and some were not given access to a running wheel until 2 weeks post-injury. The rats that were given access to a running wheel immediately did not show positive molecular markers of plasticity and they performed worse on behavioral tasks. The rats that were given access to a running wheel from 14–21 days post-injury did show the positive molecular markers and they performed better on the behavioral tasks. Griesbach and colleagues (Griesbach, Gomez-Pinilla, & Hovda, 2007) utilized a similar methodology but examined both mild and moderate brain injuries. The findings for mild injury were replicated, but moderately injured rats needed to rest longer before they benefited from exercise.

In a recent study, however, Griesbach and colleagues (Griesbach, Hovda, Gomez-Pinilla, & Sutton, 2008) obtained results that ran somewhat contrary to their previous work. This study involved a different mechanism of injury (i.e., a cortical contusion injury versus a fluid percussion injury). Molecular improvement *did* occur in injured rats that exercised during the *first week*. However, they did most of their exercising in the last 3 days of that week—they exercised less than the sham rats in the initial days.

Taken together, the series of studies by Griesbach and colleagues suggests that exercise is good for the brain, even the injured brain, but there appears to be an important temporal window. That is, injured rats that exercise too soon do have suppressed molecular markers of plasticity. These studies provide basic science support for the clinical recommendation of complete rest following injury. However, these studies cannot translate directly into clinical recommendations. It is essential to appreciate that the rats first underwent neurosurgery to expose their brain, they were then rendered unconscious (and they typically stopped breathing), and upon regaining consciousness they underwent another neurosurgical procedure prior to being returned to their cages. Uninjured rats went through the same surgical procedures to control for these effects, but the point is that it is extremely difficult to use an animal model to closely approximate a mild concussion experienced in sports or in combat.

Unfortunately, due to obvious methodological and ethical issues and challenges, there is very little research on this topic with humans. Majerske and

colleagues (2008) studied 95 student athletes who were retrospectively assigned into one of the following five groups based on their post-concussion activity level: (1) no school or exercise activity ($n=35$), (2) school activity only ($n=77$), (3) school activity and light activity at home (e.g., slow jogging, mowing the lawn; $n=57$), (4) school activity and sports practice ($n=26$), (5) school activity and participation in a sports game ($n=9$). The group that seemed to function the best cognitively was #3 (school and light activity at home) and the group that functioned the worst cognitively was #5 (school and return to competition). This quasi-experimental retrospective cohort study is interesting and provocative, but does not allow causal inferences. It suggests a relation, however, between activity level and cognitive functioning acutely and post-acutely following injury.

New insights from functional imaging studies

Animal studies have described the complex neuropathological processes that come into play following even mild central nervous system (CNS) trauma (Farkas & Povlishock, 2007; Raghupathi, 2004). There have also been several reports of neuropathological findings shortly after MTBI in humans who died of other causes (Bigler, 2004; Blumbergs et al., 1994, 1995; Goodman & Mattson, 1994; Oppenheimer, 1968). Neuroimaging, however, has been the mainstay of attempts to understand the neuropathophysiology of human MTBI. A full discussion of these efforts is beyond the scope of this paper but has been detailed in recent reviews (Belanger, Vanderploeg, Curtiss, & Warden, 2007; Levine et al., 2006). Of particular interest are techniques that shed light on two groups: (a) individuals studied shortly after injury who have normal conventional structural imaging (such as CT scan or structural MRI), and (b) individuals who do not show the typical recovery pattern.

Two MRI-based techniques show particular promise: diffusion tensor imaging (DTI) and magnetization transfer imaging. DTI is of particular interest in that it is sensitive to subtle changes in white matter integrity. Arfanakis and colleagues (2002) reported that five individuals studied within 24 hours of a MTBI showed reduced fractional anisotropy (FA: a measure of white matter integrity) that was most commonly seen in the corpus callosum and internal capsule. Follow-up scans 1 month later in two of the individuals showed improvement but not complete normalization of the FA values. Inglese and colleagues (Inglese, Benedetti, & Filippi, 2005) studied 46 patients with MTBI (20 of whom within 5 days of injury) and 29 healthy controls. Both MTBI groups showed reduced FA and increased mean diffusivity in the corpus callosum, the internal capsule, and the centrum semiovale. Kraus and colleagues (2007) performed DTI in 37 individuals with a history of TBI of different severities, 20 of whom had MTBI by American Congress of Rehabilitation Medicine criteria (Kay et al., 1993). Compared to 18 healthy controls, the MTBI group showed reduced FA in three of 13 regions of interest including the cortico-spinal tract, sagittal striatum, and superior longitudinal fasciculus. Of note is that the MTBI group was studied a mean of 92.5 months after injury and had a mean loss of consciousness of about 5 minutes. Of particular interest is that FA values have been shown to correlate with cognitive performance

(memory, attention, reaction time) in both healthy controls and individuals with a history of MTBI (Niogi et al., 2008a, 2008b).

Bagley and colleagues (2000) and McGowan et al. (2000) have used magnetization transfer imaging to show regional brain abnormalities following MTBI in regions consistent with known neuropathological vulnerability (corpus callosum). In both studies those individuals with persistent cognitive complaints had demonstrable abnormalities on imaging. In the Bagley study the patients were studied within 1 month of injury. In the McGowan study they were studied within “months” of their injuries and had persistent cognitive complaints.

Functional MRI (fMRI) has been used to study neural mechanisms of cognitive function after MTBI. In a fMRI study of 15 concussed high-school football athletes within 18 hours of injury, Hammeke et al. (2004) found decreased activation in the supplementary motor (SMA) and pre-SMA during a memory scanning paradigm when compared to a matched group of uninjured athletes. The decreased activation occurred largely in players who had a loss of consciousness from their injury and was related to a generalized slowing of selective reaction time. When studied 45 days following injury, the task activation pattern in the concussed players had normalized.

McAllister and colleagues (McAllister, Flashman, McDonald, & Saykin, 2006; McAllister et al., 1999, 2001) have suggested that 1 month after MTBI patients show a mismatch of activation and allocation of working memory processing resources, despite cognitive performance that is equivalent to that of healthy controls. Chen and colleagues (2004) also reported abnormal cerebral activation patterns in 16 concussed athletes studied 1–14 months after injury; 15 of the athletes were symptomatic at the time of study. Although performance on the task did not differ from controls, the concussed group showed reduced activation in frontal cortex and increased areas of activation in parietal and temporal regions relative to the controls. This group (Chen, Johnston, Petrides, & Ptito, 2008) subsequently reported on nine concussed athletes with persistent post-concussive complaints studied on two occasions; 1–9 months after injury and again 9–23 months after the first study. Compared to healthy controls ($n=6$), the concussed group initially showed reduced dorsolateral prefrontal cortical (DLPFC) activation associated with a working memory task. When reassessed, those concussed athletes whose symptoms had largely resolved ($n=4$) showed some increased left DLPFC activation relative to the unimproved group. Jantzen and colleagues (Jantzen, Anderson, Steinberg, & Kelso, 2004) found increased activation associated with cognitive tasks in four concussed athletes (compared to baseline studies and non-concussed teammates) within a week of injury. Cognitive performance was equivalent between the two groups. More recently, Lovell and colleagues (2007) also found increased medial frontal and temporo-parietal activation associated with a working memory task in 28 concussed student athletes studied about 1 week after injury. Furthermore the degree of activation in this region correlated with length of time to return to play.

In summary, inferences from the above studies must be considered tentative at best in that there are no large-scale longitudinal studies of individuals with MTBI using the most sensitive available neuroimaging techniques. Variable methods across studies also limit the ability to determine to what extent

neuroimaging findings may be influenced by pre-injury differences or co-morbidities. Nevertheless, some tentative conclusions seem reasonable. The first is that with each advance in imaging technology comes an increase in the sensitivity to detect abnormalities in brain structure and function in the first days to several weeks after MTBI. For example conventional MRI demonstrates more lesions than CT scan (Bigler, 2005), and more recent MRI-based techniques are more sensitive than the initial T1 and T2 weighted images. Within the first month after injury, functional imaging, particularly PET and fMRI show changes in task-associated brain activation even in the absence of abnormal structural imaging. Studies with longer intervals between injury and assessment are more variable. Nevertheless the recent DTI studies showing increased regions of white matter abnormalities relative to non-injured controls, and correlation of performance with these white matter abnormalities in regions that are biologically plausible, suggest that some longer lasting effects of MTBI may be seen in some individuals.

Still, although interpretation of the relationship between persisting symptoms and markers of brain abnormalities noted above seems straightforward when the brain abnormalities are structural in nature (e.g., FA from DTI), more caution is needed when the brain abnormalities are derived from functional imaging techniques because the persisting symptoms may perturb the imaging signal in indirect ways (e.g., be a source of attentional distraction during the imaging study). It is also important to point out that although performance after MTBI may return to “normal,” the effort required to achieve that performance may be greater than expected, giving rise to a sense of reduced cognitive capacity, and, theoretically, reduced cognitive reserve. Larger longitudinal studies are required to examine these impressions. Additional research is also needed to better understand the natural evolution of brain-related functional adaptation and compensatory mechanisms over time following injury, and to determine why some individuals have persisting brain abnormalities and others do not.

AN INTEGRATED MODEL OF MTBI RECOVERY

Our scientific understanding of MTBI has arguably progressed more in the past decade than it had in the prior 50 years, and now reaches an exciting maturity point where key findings from every corner begin to converge and ultimately bring applied value to clinical practice. Overall, the evidence base reviewed herein on the natural history of clinical and neurophysiological recovery after MTBI begins to establish the foundation for an integrated model of MTBI recovery.

As described earlier, findings from large, prospective studies now illustrate that post-concussion symptoms, cognitive dysfunction, and other functional deficits are most severe during the earliest acute period after MTBI, then follow a gradual, overlapping course of recovery beginning within hours of injury and completely resolve within days to weeks in the overwhelming majority of cases. In the case of neuropsychological recovery, meta-analytic studies demonstrate essentially undetectable effect sizes beyond roughly 2–4 weeks after MTBI.

Technological advances in functional imaging have created a powerful bridge between traditional clinical and basic science studies of MTBI. A particularly interesting picture begins to emerge when looking at the collective findings from fMRI studies of acute, subacute, and chronic MTBI. In brief, findings from functional imaging studies now begin to form a hypothesis that MTBI physiologically manifests in a pattern of decreased cerebral activation in select attention-related neural circuits during the earliest acute period (e.g., 12–24 hours post-injury) that perhaps relates to the acute physiological mechanisms of injury. Increased activation is then evident during the subacute phase (e.g., 1 month post-injury) that appears to relate to compensatory mechanisms, and there is a return to normal activation patterns further out from injury (e.g., >30 days post).

Without question, the evolution of functional imaging technologies has yielded steady gains in our understanding of the mechanisms of functional and structural abnormalities in human MTBI. Still, it should be noted that most studies to date have involved quite heterogeneous groups of MTBI patients and applied variable methods of study that make it difficult to draw global inferences across the literature.

Collectively, findings from clinical research, basic science, and functional imaging studies converge on the true natural history of single, uncomplicated MTBI across the full time course from minutes to months post-injury. Although far from conclusive at this point, these recent advances have now brought the science of MTBI to a point at which we begin to form theories and testable hypotheses around a comprehensive model of MTBI recovery (see Table 1).

At a practical level, this theoretical recovery model adds to our perspective on the direct experience of the MTBI patient. These patients often report rather severe signs and symptoms that render them largely inactive for the initial days after uncomplicated MTBI, followed by a period during which they return to school or work but feel they have to expend a great deal more mental energy to function at their customary level (which in turn may be accompanied by fatigue or diminished endurance). They then most often resume all their routine activities within 2–6 weeks after injury, without major difficulty or need for accommodations.

Admittedly, this model does not fully explain those cases that fail to follow a typical recovery course and report chronic symptoms or functional impairments after MTBI. It is known that symptoms of depression, anxiety and post-traumatic stress disorder (PTSD) are often mistaken as chronic effects of MTBI. Management strategies should focus on properly identifying and treating these conditions. Reports from systematic reviews of the treatment literature have found little evidence that neurological therapies, including drug interventions or cognitive remediation, are effective for individuals with MTBI (Borg et al., 2004; Comper, Bisschop, Carnide, & Tricco, 2005). However, there is evidence that psychological approaches to treatment, consisting of supportive or educational interventions, are effective in helping individuals to recover from MTBI and these associated conditions. Routine use of these psychological interventions early in recovery, combined with gradual but early return to normal activities following MTBI,

Table 1 Integrated model of recovery after uncomplicated MTBI

Acute Period (immediately after injury to ~5 days post):

- Symptoms and cognitive impairments can be severe and significantly disrupt normal daily function
- The brain is sufficiently injured to create a neurometabolic crisis. Functional neuroimaging studies can reveal a dysregulation of normal and consistent recruitment of neuronal resources (e.g., decreased activation)
- Exertion while the brain is in a state of neurometabolic crisis may slow down recovery and, theoretically, could have other secondary pathophysiological effects

Subacute Period (~5–30 days post)

- Symptoms and cognitive/functional impairments follow a gradual, overlapping course of improvement
- Clinically, an overwhelming majority of cases achieve full symptom and neuropsychological recovery
- Neurophysiologically, the brain continues on a course of recovery to a normal metabolic state and cerebral functioning, during which over-recruitment of neuronal resources may be required to achieve customary functional and performance standards (e.g., increased activation on functional neuroimaging)
- Once asymptomatic, a protocol of gradual, sequential exertion is appropriate, initially focusing on cardiovascular challenge before transitioning to more vigorous exercise

Chronic Period (>30 days post)

- A relatively small percentage of patients report persistent symptoms and cognitive or other complaints, which may be influenced by injury (e.g., more severe grades of complicated MTBI with abnormal structural imaging findings) or non-injury related factors (e.g., depression, PTSD, chronic pain, life stress, or secondary gain)
- The brain returns to a normal state of cerebral function (e.g., normal activation on functional neuroimaging) in the overwhelming majority of cases
- Persistent post-concussion symptoms may be observed in a small percentage (<5%) of MTBI cases, significantly influenced by non-injury-related factors
- If identified, co-morbidities (e.g., depression, anxiety, PTSD, chronic pain, etc.) should be treated. Psychological and educational interventions can be effective in improving functional outcome and reducing persistent disability from MTBI and these associated conditions

This theoretical model applies to a single, uncomplicated MTBI without focal, structural injury visualized on conventional neuroimaging (e.g., CT, MRI) and is less relevant in more severe forms of MTBI or repeat MTBI. This model does not apply to moderate or severe TBI.

can provide an effective means to avoiding the long-term consequences of postconcussion syndrome (Ponsford, 2006).

IMPLICATIONS FOR CLINICAL MANAGEMENT OF MILITARY-RELATED MTBI

In keeping with the theme of this special issue of *The Clinical Neuropsychologist*, our ultimate aim is to transfer the evidence base on the acute effects and true natural history of recovery after MTBI to a useful framework for the clinician charged with the challenging assignment of evaluating and managing military personnel affected by MTBI. Clearly, delivering a detailed clinical practice guideline or algorithm for management of military-related MTBI is beyond the scope and authority of this review. Likewise, it is unrealistic for us to appreciate

all the military operational implications of clinical management, particularly in an austere environment.

We can, however, perhaps draw several parallels from our theoretical model of MTBI recovery to clinically useful considerations for the evaluation and management of military personnel affected by MTBI:

- (1) MTBI is likely to cause significant symptoms and functional impairments during the first several days that not only negatively impact a warrior's ability to fulfill their duties, but may also place the individual at considerable risk of recurrent injury or further harm.
- (2) There is basic science evidence that exercise too soon after MTBI could, at minimum, slow down the recovery process. It is less clear, but certainly possible, that vigorous exercise while the brain is in acute neurometabolic crisis could compound secondary pathophysiologies and more seriously disrupt neuroplasticity. Therefore, it is likely advisable for injured military personnel to avoid mental and physical exertion in the initial days following uncomplicated MTBI. Once asymptomatic, the injured person should begin a gradual, sequential exertion protocol focusing initially on cardiovascular challenge (e.g., stationary bike or light jogging) before transitioning to more vigorous exercise (e.g., running or supersets of pushups, situps, jumping jacks, etc.)
- (3) Clinical recovery (i.e., as measured by imperfect instruments such as symptom checklists) may not fully equate to true recovery at a brain level (i.e., completely normal cerebral functioning). The main concern here is that there may be a window of neurobiological vulnerability during which the injured warrior remains functionally disadvantaged or susceptible to the ill effects of repeat concussion, even after reaching full clinical recovery. Unfortunately, we have not yet reached a point at which we have a perfect biological marker of concussion (and subsequent recovery) for clinical use. No doubt, ongoing technological advancements in neuroimaging and other areas of neuroscience show great promise, but will face unique challenges of practicality before being adopted for clinical use in the military theater. Until then, the use of standardized methods (e.g., neuropsychological testing) to *measure* recovery and to determine readiness to return to duty is recommended, rather than simply relying on a warrior's self-reported symptom recovery.
- (4) The literature supports a biopsychosocial approach to the management of individuals with chronic symptoms or functional complaints reflective of postconcussion syndrome after MTBI. This is especially relevant in a military setting where post-traumatic stress disorder (PTSD), depression, anxiety, chronic pain, and other comorbidities known to complicate recovery after MTBI are highly prevalent (Hoge, Auchterlonie, & Milliken, 2006; Hoge et al., 2008). These comorbidities can mimic (or, possibly, obscure) residual effects of MTBI (see Iverson, Zasler, & Lange, 2007b, for review). Successful injury management will require attention to the diagnosis and treatment of psychological disorders in the context of MTBI.

In conclusion, major advancements in the clinical and basic science of MTBI now provide a more sound evidence base for clinical management in both civilian and military sectors. Further study is required to confirm or refute theoretical

models of MTBI recovery. Much as was the case with sport-related concussion, well-planned prospective studies on the acute effects, recovery, and outcome after military-related MTBI will not only directly benefit military medicine experts, but also provide great value to the larger neurosciences by advancing the science of MTBI in the general population.

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BAILES

EXHIBIT 8

Standard regression-based methods for measuring recovery after sport-related concussion

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Abstract

Clinical decision making about an athlete's return to competition after concussion is hampered by a lack of systematic methods to measure recovery. We applied standard regression-based methods to statistically measure individual rates of impairment at several time points after concussion in college football players. Postconcussive symptoms, cognitive functioning, and balance were assessed in 94 players with concussion (based on American Academy of Neurology Criteria) and 56 noninjured controls during preseason baseline testing, and immediately, 3 hr, and 1, 2, 3, 5, and 7 days postinjury. Ninety-five percent of injured players exhibited acute concussion symptoms and impairment on cognitive or balance testing immediately after injury, which diminished to 4% who reported elevated symptoms on postinjury day 7. In addition, a small but clinically significant percentage of players who reported being symptom free by day 2 continued to be classified as impaired on the basis of objective balance and cognitive testing. These data suggest that neuropsychological testing may be of incremental utility to subjective symptom checklists in identifying the residual effects of sport-related concussion. The implementation of neuropsychological testing to detect subtle cognitive impairment is most useful once postconcussive symptoms have resolved. This management model is also supported by practical and other methodological considerations. (*JINS*, 2005, *11*, 58–69.)

Keywords: Brain injury, Brain concussion, Athletic injuries

INTRODUCTION

Sport-related concussion is now widely recognized as a major public health concern in the United States and worldwide (Aubry et al., 2002; Collins et al., 1999; Kelly, 1999). The Centers for Disease Control and Prevention report that approximately 300,000 sport-related concussions occur annually in the United States (Thurman et al., 1998), and

recent data from the National Collegiate Athletic Association (NCAA) Injury Surveillance System reveal that concussion is amongst the most frequently observed injuries in collegiate ice hockey, football, and soccer (Dick, 2003). Epidemiological and prospective clinical studies estimate that approximately 3% to 8% of high school and collegiate football players sustain a concussion each season (Collins et al., 1999; Echemendia et al., 2001; Guskiewicz et al., 2000, 2003; Macciocchi et al., 1996; McCrea et al., 1997, 1998, 2002; Powell & Barber-Foss, 1999), and the rate of documented concussion in collegiate football has been on the rise in recent years (Covassin et al., 2003; Dick, 2003).

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Sports medicine professionals consider diagnosing concussion and determining postinjury recovery among their greatest clinical challenges, especially when confronted with intense pressure to formulate a rapid assessment of injury and prompt decision about how soon an athlete can safely return to competition (Cantu, 1986; Kelly, 1999; Vastag, 2002). Despite a growing body of research, there remains little evidence-based guidance on how long it takes for an athlete to recover and deciding when it is safe for the athlete to return to play after a concussion. Existing guidelines largely stem from expert consensus, with limited scientific support from prospective studies (Aubry et al., 2002; Kelly, 1999; Vastag, 2002). As a result, sports medicine clinicians have historically relied on their experience and subjective observations to track postinjury recovery and guide clinical decision making about return-to-play.

Neuropsychologists have made a significant contribution to advancing the scientific understanding of the effects and expected recovery course after sport-related concussion (Echemendia & Julian, 2001). Several neuropsychological studies have reported estimates of recovery in symptoms and cognitive dysfunction ranging from several hours to several days (Collins et al., 1999, 2003; Echemendia et al., 2001; Erlanger et al., 2003; Hinton-Bayre et al., 1999; Lovell et al., 2003; Macciocchi et al., 1996; Maddocks & Saling, 1996; McCrea, 2001; McCrea et al., 1998, 2002). Interpretation of recovery data across studies has been hampered by a number of methodological factors, however, including small sample sizes, varied definitions of concussion, absence of an immediate injury assessment to measure the most acute effects, limited follow-up assessment of injured players, failure to establish a recovery endpoint, and lack of an appropriate control group. The findings from a recent 3-year prospective study demonstrated that collegiate football players, on average, followed a gradual course of recovery in symptoms, cognitive functioning, and postural stability over the first 5–7 days after concussion, but that 10% of injured players required more than 7 days to reach a full recovery (McCrea et al., 2003). The study focused on analysis of group effects, limiting the application of the findings to actual clinical decision making in individual cases.

There has been a growth of recent interest in defining the most clinically useful methods for detecting change in neuropsychological test scores in test–retest situations. The emphasis has been to move beyond analysis of group statistics toward the detection of change in individual participants. Much attention has focused on the use of the reliable change index (RCI) and standardized regression-based (SRB) methods, which are techniques initially developed and refined in studies of outcome from psychotherapy and surgical treatment. Conclusions drawn from recent reviews indicate that, while RCI methods may be easier to use in a clinical setting, SRB methods are demonstrated to be more accurate for detecting meaningful change as a result of their ability to correct for practice effects, regression to the mean, and the impact of baseline test performance. The SRB methods

are thus recommended for use in research settings examining test–retest changes (Barr, 2002; Temkin et al., 1999).

Techniques to more precisely measure and characterize meaningful and reliable change in neurocognitive test performance in individual patients over time are especially intriguing in the case of sports concussion assessment. The prototypic sports concussion assessment model implemented in many professional, collegiate, and high school athletic programs incorporates a preseason baseline evaluation of all players that includes a clinical history, base rate symptom index, neurocognitive battery, and postural stability testing. Any player who sustains a concussion over the course of the season is then reevaluated with these measures at several time points, initially to determine the severity of their injury and then track their postinjury recovery. Clinical research programs also include matched, non-injured controls in the identical testing protocol. Despite the methodological advantages of this model, serial testing of injured athletes presents the clinician with the challenge of distinguishing between “real” change in individual test performance indicative of true recovery *versus* performance variability due to practice effects, measurement error, or random influence.

The current study sponsored by the NCAA applied a serial testing paradigm and regression-based methods to statistically define recovery and measure individual rates of impairment at several time points after concussion in collegiate football players.

METHODS

Research Participants

A total of 1631 football players from 15 National Collegiate Athletic Association (NCAA) Division I, II, and III member institutions were enrolled in one arm of a larger cohort study of the effects of sports-related concussion from 1999 through 2001. In total, 2410 player seasons were analyzed, as 779 players were enrolled for more than 1 year of the study. A case series of 94 injured players who sustained a concussion (5.76% of players, 3.90% of player seasons) were enrolled in an extensive injury assessment protocol. No player who sustained a concussion refused to participate or was excluded from the study protocol, but information on unidentified or unreported concussions was not available.

Fifty-six noninjured controls matched to injured participants on the basis of age, years of education, team, and baseline performance on concussion assessment measures were administered the identical protocol under the same conditions and retest intervals as injured players during the first year of the study. Limited resources did not allow enrollment of additional control participants in years 2 or 3 of the study, which had a minimal effect on matching characteristics for the complete study sample. Table 1 provides a comparison of demographic and medical history data for the injured and control groups.

Table 1. Concussion and control group characteristics

	Concussion (<i>n</i> = 94)		Control (<i>n</i> = 56)		Mean Diff.	<i>t</i>	<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>			
Demographics:	73.50	2.94	72.75	3.23	.75	1.44	.151
Weight (lbs.)	235.26	46.88	218.50	46.19	16.76	2.11	.037*
Age (years)	20.04	1.36	19.20	1.45	.84	3.51	.001*
Academic year (collegiate)	2.78	1.18	2.02	1.23	.76	3.71	.001*
Self-reported history of:							
No. of previous concussions (past 7 years)	.58	.78	.39	.68	.19	1.47	.145
Range	0–5		0–3				
Any concussion (lifetime) (%)	43.2		30.4		$\chi^2 = 2.78$.123
ADHD (%)	2.30		1.80		$\chi^2 = .034$.854
Learning disability (%)	2.30		1.80		$\chi^2 = 1.64$.440

Notes. *Statistically significant. ADHD = Attention Deficit Hyperactivity Disorder. LD = Learning Disability.

This study was approved by the Institutional Review Board (IRB) for protection of human research participants at the host institutions of the principal investigators. All participants granted written informed consent prior to enrollment in the study.

Study Design

All players underwent a preseason baseline evaluation on a battery of concussion assessment measures and extensive health questionnaire prior to their first year of participation in this study. Injured participants were identified and enrolled in the study protocol by a team physician or certified athletic trainer present on the sideline during an athletic contest or practice. *Concussion* was defined as an injury resulting from a blow to the head causing an alteration in mental status and one or more of the following symptoms prescribed by the American Academy of Neurology Guideline for Management of Sports Concussion (Practice Parameter, 1997): headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, or difficulty concentrating (Kelly & Rosenberg, 1997). Loss of consciousness (LOC), posttraumatic amnesia (PTA) (e.g., inability to recall exiting the field, aspects of the examination, etc.), and retrograde amnesia (RGA) (e.g., in ability to recall aspects of the play, events prior to injury, score of the game, etc.) were documented immediately after injury.

All players identified by the team physician or certified athletic trainer as having sustained a concussion according to the study's injury criteria were tested with a Graded Symptom Checklist (GSC) (Lovell & Collins, 1998), the Standardized Assessment of Concussion (SAC) (McCrea et al., 2000), and the Balance Error Scoring System (BESS) (Guskiewicz et al., 2001) on the sideline immediately following injury. Follow-up testing on these measures was then conducted postgame/postpractice (2–3 hr after injury), and again on postinjury days 1, 2, 3, 5, and 7. The brief

neuropsychological test battery (see Table 2) was administered to assess neurocognitive functioning at baseline and on days 2 and 7 postinjury. A day-90 assessment point was also included in the original design, but significant attrition for both injured and control participants did not allow application of the standard regression-based methods employed in this study for this assessment point. Assessments were conducted by certified athletic trainers who were trained by the researchers and required to watch a training video on administration and scoring of all outcome measures used in the study.

Main Outcome Measures

A summary of the main outcome measures used in this study to assess postconcussive symptoms, cognitive functioning, and postural stability is provided in Table 2. Several studies on the effects of sport-related concussion have demonstrated the reliability and accuracy of the GSC (Lovell et al., 2003), SAC (Barr & McCrea, 2001; McCrea, 2001), BESS (Guskiewicz et al., 2001; Riemann et al., 1999; Riemann & Guskiewicz, 2000), and components of the neuropsychological test battery (Collins et al., 1999) in correctly classifying injured and noninjured participants after concussion.

Statistical Analysis

There was limited missing data, with 93% of data cells complete across all time points for all participants. To examine the potential effect of missing data on the results, we compared the baseline scores for the missing and nonmissing participants at every time point for all outcomes. The baseline scores did not differ between missing and nonmissing, suggesting that the data was missing at random (Diggle et al., 1994). As part of our previous analysis (McCrea et al., 2003), we also estimated the missing data using a single imputation model (Rubin, 1976, 1996; Schafer, 1997), based on time, participants status (injured vs. control), and

Table 2. Assessment measure characteristics

Measure	Functional domain	Description	Score range	Time to administer
Graded Symptom Checklist (GSC)	Postconcussive symptoms	Subject rates presence and severity of 17 symptoms (e.g., headache, dizziness, etc.)	0 (no symptoms)–6 (severe) Likert scale per item; total score range: 0–102; higher score indicates more severe symptoms	2–3 min
Standardized Assessment of Concussion (SAC)*	Cognitive functioning: - orientation - immediate & delayed memory - concentration Neurologic Screening: - strength - sensation - coordination	Brief neurocognitive assessment and neurologic screening; documentation of unconsciousness, posttraumatic amnesia, retrograde amnesia	Total score range: 0–30; lower score indicates more severe cognitive impairment	5 min
Balance Error Scoring System (BESS)	Postural stability	Noninstrumented, clinical assessment of postural stability in double leg, single leg, tandem stances on firm and foam surfaces	No defined range; test score equals total number of errors committed by the participant; higher score indicates more severe postural instability	5 min
Neuropsychological Test Battery*	Cognitive functioning: - attention - concentration - processing speed - mental flexibility - anterograde memory	Hopkins Verbal Learning Test Trail Making Test Part B Symbol Digit Modalities Test Stroop Color-Word Test Controlled Oral Word Association Test	Total score range based on individual measures; lower score indicates more severe impairment except for Trail Making Test (total time to complete)	25 min

*Alternate forms utilized to minimize practice effects practice effects from repeat testing on SAC and neuropsychological test battery.

baseline test performance, and obtained essentially identical results on separate analysis of the nonimputed and imputed data.

Group recovery data analyses have been published previously (McCrea et al., 2003), including illustrations of the natural course of recovery in symptoms, cognitive dysfunction, and balance problems following concussion. Those analyses utilized Generalized Estimating Equations (GEE) to examine the adjusted group mean differences on each assessment measure at each assessment point, while controlling for baseline test performance and other factors known to influence performance on specific measures (e.g., years of education on cognitive testing).

The current data analysis focused on individual rates of impairment, rather than generating group recovery curves on each of the study's main assessment measures. Classification of impairment at the individual case level was based on an empirical method using SRB indices for detection of significant change in test scores (McSweeney et al., 1993; Temkin et al., 1999). This method uses linear regression on baseline scores from the healthy control group to generate a formula for predicting follow-up scores at various time points. The resulting regression coefficient and the intercept of the regression line were used with the baseline score to compute a predicted score for each participant at Time 2 and at subsequent testing points. This approach provides an empirical method for detecting meaningful change while also providing correction for practice effects and regression to the mean.

Participants were considered to have undergone a meaningful change in test performance if the difference between the obtained and predicted score, divided by the standard error of prediction, was larger than a specific criterion value, translated to a 90% confidence interval (two-tailed, 5% chance of Type I error). Predictions for the GSC, BESS, and SAC were computed for all time points from the time of injury through day 7. Predicted scores for each of the neuropsychological tests were computed for days 2 and 7. Based on the conventional standard within neuropsychology and to minimize the rate of false positives, impairment on the neuropsychological test battery was defined as having significantly decreased scores on two or more tests. Conservatively assuming complete orthogonality among outcome measures, which is not likely the case due to shared group variance across measures, the expected rates of false positives (identifying a normal participant as impaired) ranged from 5% for a single measure to 15% for impairment on any one of three measures (e.g., impairment on the brief battery of the GSC, BESS, and SAC), and ranged up to 27.3% when adding the criterion of impairment on two of the seven measures in the neuropsychological test battery.

Frequencies were also generated for the percentage of participants who had reached a full symptom recovery based on GSC score, but continued to show impairment on the BESS, SAC, or the neuropsychological test battery on post-injury days 2 and 7, based on the respective SRB indices for each test.

Measures of sensitivity and specificity were computed for establishing each test's ability to distinguish between the injured and control groups. In this context, sensitivity (Se) refers to the probability that an injured participant will be identified as "abnormal" by a change in test performance. At time points subsequent to time of injury, sensitivity values indicate the probability that a player originally injured continued to be classified as "abnormal" according to at least one of the test measures. Specificity (Sp) refers to the probability that a control participant will be correctly classified as "normal" using the same method. Data were analyzed with SPSS 11.0 statistical software (SPSS, 1999).

RESULTS

Ninety-four players who sustained a concussion during football practice (56.8% of injuries) or games (43.2%) were studied. Most injuries were classified as either Grade 1 or 2 concussions according to the Cantu (Cantu, 1998) (98.6%), Colorado (Colorado Medical Society, 1991) (93.3%), and American Academy of Neurology (Practice Parameter, 1997) (93.2%) sports-concussion grading scales, based on our *post-hoc* review of injury characteristics. A small number of injured participants sustained LOC (6.4%; median duration 30 s). Additionally, a small percentage of participants exhibited PTA (19.1%; median duration 90 min) or RGA (7.4%; median duration 120 min). There was no LOC, PTA, or RGA associated with most injuries (77.8%). Ninety injured participants (96%) completed the assessment protocol through the day 7 assessment point.

Results from group (concussion vs. control) data analyses on the GSC, BESS, SAC, and neuropsychological test battery have been reported previously, including illustrations of the pattern of recovery in symptoms, cognitive functioning, and postural stability (McCrea et al., 2003). As context for interpretation of the current results from the SRB analysis, raw means for the concussion and control groups on the GSC, BESS, and SAC at baseline and each postinjury assessment point are provided in Table 3, and group data from the neuropsychological test battery are provided in Table 4.

Results from the current analyses focus on the rate of recovery by individual players with concussion. The percentages of injured participants and controls impaired at each assessment point on the GSC, SAC, BESS, and neuropsychological test battery, as defined for each test according to the SRB calculation, are presented in Figure 1. During the acute postinjury period, the highest rate of abnormality was observed on the GSC, with 89% of the sample reporting increased symptoms at the time of injury and 74% reporting symptoms 1 day later. There was a gradual decline in the percentage of participants with elevated GSC scores on ensuing days, with only 4% reporting significant symptoms 1 week after concussion. The base rate of common concussive symptoms in the control group was zero across all assessment points.

Table 3. GSC, SAC, and BESS data for concussion and control groups at baseline and postinjury assessment points

	GSC				SAC				BESS			
	Concussion		Control		Concussion		Control		Concussion		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	1.97	4.94	.99	3.26	27.37	2.16	27.43	1.77	11.95	8.09	12.73	7.57
Time of concussion	20.60	10.58	.20	2.54	24.94	3.07	27.69	1.91	19.46	9.48	12.34	9.06
Postgame/ postpractice	16.73	11.86	.18	1.96	25.58	3.03	27.76	1.85	16.70	9.16	12.49	9.32
Day 1	12.25	12.52	.18	.69	26.25	2.79	27.96	1.65	14.18	8.04	11.96	8.11
Day 2	7.63	10.55	.06	.45	27.44	2.32	28.02	1.51	12.96	7.26	11.20	9.40
Day 3	6.03	10.26	.04	.44	27.57	2.46	27.96	1.64	12.31	7.80	11.29	7.71
Day 5	3.06	5.95	.04	.47	28.02	3.24	28.73	1.40	10.97	6.78	11.69	7.95
Day 7	1.27	3.37	.02	.46	28.41	1.85	28.37	3.39	9.67	6.88	10.93	8.21

GSC = Graded Symptom Checklist (Lovell & Collins, 1998); SAC = Standardized Assessment of Concussion (McCrea et al., 2000); BESS = Balance Error Scoring System (Guskiewicz et al., 2001).

Acute cognitive dysfunction, as measured by impairment on the SAC, was evident in 80% of the injured sample at the time of concussion. Persistent cognitive impairment was seen on the SAC in 31% of the injured sample on day 1, 23% on day 2, and 9% (essentially at control levels) on day 7. Statistically defined abnormality on the SAC ranged from only 5–9% of the control group across all assessment points. Similarly, examination of the neuropsychological test results indicates that 23% of concussed players were impaired on two or more measures on postinjury day 2 and 17% were impaired on day 7. Eight percent of control participants were impaired on two or more measures at day 2, and 9% on day 7. Analyses of individual neuropsychological test scores on days 2 and 7 indicate that the largest percentage of injured participants obtained abnormal test scores on measures of delayed recall and recognition memory (HVL Delayed Recall and Recognition), cognitive processing speed (Trails B, Symbol Digit Modalities Test), and verbal fluency (COWAT).

Impairments in postural stability, as defined by poorer performance on the BESS, were seen in 36% of the injured participants immediately following concussion, compared to 5% of the control group. Twenty-four percent of injured

participants remained impaired on the BESS on day 2, compared to 9% by day 7 postinjury. Table 5 presents the rates of impairment in concussion and control groups for the composite battery of brief measures (GSC, BESS, SAC) at all time points, and the addition of neuropsychological testing at postinjury days 2 and 7.

Sensitivity and specificity values are provided for each measure in Table 6. The results indicate that the GSC provided the most sensitive ($Se = .89$) and specific ($Sp = 1.00$) measure of abnormality at the time of injury. The specificity values remained at 1.00 at each time point thereafter, indicating that none of the controls exhibited a significant increase in self-reported symptoms at any time point. Sensitivity values for the BESS were highest at the time of injury ($Se = .34$). Specificity values for this instrument ranged from .91 to .97 across the various time points. A similar pattern of data was obtained with the SAC, with a peak sensitivity value of .80 at the time of injury and specificity values ranging from .89 to .98 through day 7. The neuropsychological test battery classified injured participants with sensitivity values of .23 and .19 at days 2 and 7, respectively. Specificity values were .93 and .91.

Table 4. Neuropsychological test data for concussion and control groups at baseline and postinjury days 2 and 7

	Baseline				Day 2				Day 7			
	Concussion		Control		Concussion		Control		Concussion		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HVLT Immediate Memory	25.03	4.36	25.31	4.05	24.42	4.52	25.42	4.37	25.56	4.26	26.17	4.59
HVLT Delayed Recall	8.61	2.18	9.15	2.13	8.11	2.68	8.84	2.48	8.50	2.65	10.29	5.88
HVLT Recognition	22.60	1.97	22.94	1.26	22.20	1.88	22.95	1.52	22.50	1.54	22.77	2.39
Trail Making Test, Part B	64.42	22.22	57.30	18.69	59.70	21.20	51.33	16.67	53.30	20.49	42.05	15.36
SDMT	55.56	11.61	58.90	12.19	55.05	11.21	62.23	13.76	55.00	10.35	61.65	13.35
Stroop CW Trial	47.21	9.23	48.66	9.75	47.94	11.68	51.50	9.61	53.33	11.34	55.86	10.77
COWAT	40.46	12.36	37.15	10.61	40.17	10.99	40.22	10.12	41.45	10.96	42.44	10.07

HVLT = Hopkins Verbal Learning Test (Shapiro et al., 1999); Trail Making Test (Reitan & Wolfson, 1985); SDMT = Symbol Digit Modalities Test (Smith, 1991); Stroop CW Trial = Color Word Trial (Golden, 1978); COWAT = Controlled Oral Word Association Test (Benton et al., 1983).

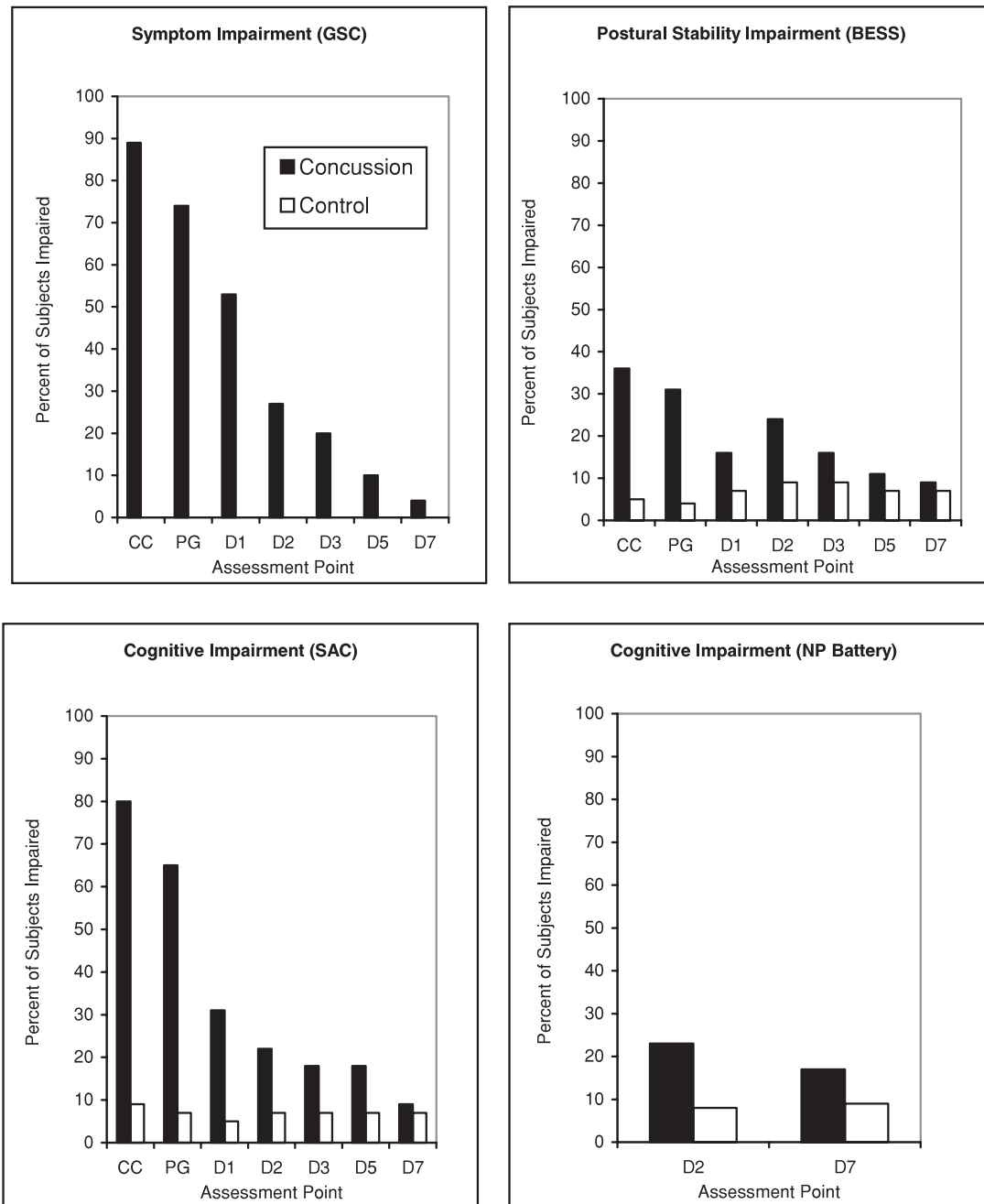


Fig. 1. Percentage of concussion and control participants classified as “impaired” from time of injury through day 7 on GSC, BESS, SAC and Neuropsychological Test Battery. GSC = Graded Symptom Checklist; BESS = Balance Error Scoring System; SAC = Standardized Assessment of Concussion; and NP Battery = Neuropsychological Test Battery. Assessment points: CC = time of concussion; PG = post-game/post-practice; D1 = postinjury day 1, D2 = postinjury day 2, etc.

An examination was made of sensitivity and specificity values for the entire battery of brief measures, defined as an abnormal score identified on either the GCS, BESS, or SAC. Again, sensitivity was highest at the time of injury, with 94% accuracy in classifying injured participants on the battery of brief measures. Specificity values ranged from .84 to .93 across the various time points. Inclusion of the neuropsychological test data barely increased the sensitivity of

the battery from .51 to .56 at day 2, with a decrease in specificity from .84 to .79. However, the neuropsychological test data more than doubled the sensitivity of the battery from .14 to .30 at day 7, accompanied by a modest increase in specificity from .79 to .86.

A small but clinically significant percentage of asymptomatic players continued to show impairment on the BESS, SAC, and neuropsychological testing on postinjury days 2

Table 5. Rates of impairment on battery of brief measures (GSC, BESS, SAC) and brief battery with neuropsychological testing

	GSC, BESS, SAC*				(GSC, BESS, SAC) + NP testing#			
	Concussion Abnormal		Control Abnormal		Concussion Abnormal		Control Abnormal	
	N	%	N	%	N	%	N	%
Time of Injury	89	95	6	11	—	—	—	—
Postgame/practice	81	86	6	11	—	—	—	—
Day 1	65	69	6	11	—	—	—	—
Day 2	48	51	9	16	53	56	12	21
Day 3	36	38	9	16	—	—	—	—
Day 5	24	26	7	13	—	—	—	—
Day 7	13	14	4	7	28	30	8	14

*“Abnormal” refers to impairment on any measure in brief battery (GSC, BESS, or SAC).

#“Abnormal” refers to impairment on any measure in brief battery or impairment on at least two neuropsychological measures.

GSC = Graded Symptom Checklist (Lovell & Collins, 1998); BESS = Balance Error Scoring System (Guskiewicz et al., 2001); SAC = Standardized Assessment of Concussion (McCrea et al., 2000); NP Testing = Neuropsychological Test Battery.

and 7 (see Table 7). The highest percentage of players reporting to be completely symptom free were impaired on the BESS on day 2, with fewer impaired on cognitive measures. On day 7, the highest percentage of asymptomatic players were impaired on neuropsychological testing, while rates of impairment on the BESS and SAC for asymptomatic players were comparable to the control group.

DISCUSSION

The current study employed standard regression-based methods combined with a baseline and serial testing paradigm to statistically measure individual rates of cognitive and functional impairment in collegiate football players after sustaining a concussion. Nearly 90% of athletes with concussion reported an increase from their baseline rate of common concussive symptoms, and 80% showed a significant decline from baseline cognitive performance during the acute post-injury period. A significant percentage of concussed players also exhibited acute impairment on postural stability

testing. The percentage of injured athletes impaired on cognitive and balance testing gradually declined over the first several days postinjury, but still remained considerably higher than the comparative rate of statistically defined impairment in matched control participants. Less than 5% of injured athletes reported higher-than-base rate postconcussive symptoms by day 7 postinjury, and rates of impairment on brief screening measures of cognitive functioning and balance were comparable for injured and noninjured participants 1 week postinjury. Seventeen percent of concussed players continued to show impairment on neuropsychological testing 1 week after injury, compared to 9% of noninjured controls.

It is also important to note that functional recovery as measured by objective testing often lagged behind the resolution of postconcussive symptoms. Most concerning was our finding that 26% of concussed players who reported being symptom free, and who presumably were eager to return to competition 1 week after their injury, continued to show measurable impairment on standardized cognitive and

Table 6. Sensitivity (Sn) and specificity (Sp) for detecting impairment at postinjury time points

	Time of injury		Postgame		Day 1		Day 2		Day 3		Day 5		Day 7	
	Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp	Se	Sp
GSC	.89	1.00	.74	1.00	.53	1.00	.27	1.00	.20	1.00	.10	1.00	.04	1.00
BESS	.34	.91	.31	.96	.16	.93	.24	.91	.16	.91	.10	.93	.07	.95
SAC	.80	.91	.65	.93	.31	.95	.22	.89	.18	.93	.18	.93	.02	.98
Brief battery without NP testing	.94	.89	.86	.89	.69	.89	.51	.84	.38	.84	.26	.87	.14	.93
NP testing	—	—	—	—	—	—	.23	.93	—	—	—	—	.19	.91
Full battery with NP testing	—	—	—	—	—	—	.56	.79	—	—	—	—	.30	.86

Notes. Sensitivity values indicate the probability that a player originally injured continued to be correctly classified as “abnormal”. Specificity (Sp) refers to the probability that a control participant will be correctly classified as “normal” using the same method.

Brief battery refers to GSC, BESS, and SAC. Full battery refers to brief battery plus neuropsychological testing.

GSC = Graded Symptom Checklist (Lovell & Collins, 1998); BESS = Balance Error Scoring System (Guskiewicz et al., 2001); SAC = Standardized Assessment of Concussion (McCrea et al., 2000); NP testing = neuropsychological test battery

Table 7. Percentage of asymptomatic participants after concussion (Sx-) and control participants classified as “Impaired” on postinjury days 2 and 7

	Day 2		Day 7	
	Sx—impaired (%) (n = 68)	Control impaired (%) (n = 56)	Sx—impaired (%) (n = 85)	Control impaired (%) (n = 56)
BESS	37	9	8	7
SAC	16	7	7	7
NP Battery	15	8	16	9

BESS = Balance Error Scoring System (Guskiewicz et al., 2001); SAC = Standardized Assessment of Concussion (McCrea et al., 2000); NP battery = neuropsychological test battery

balance testing, compared to 14% of controls. Neuropsychological testing was most sensitive to detecting cognitive impairment in otherwise asymptomatic players 1 week post-injury, with 16% impaired on at least two of the seven measures in the battery, compared to 9% of controls. These findings suggest that a period of cerebral dysfunction and vulnerability persists beyond resolution of subjective symptoms, which suggests the need for a thorough evaluation of all elements of recovery in making decisions about an athlete’s readiness for a safe return to competition.

Advanced Methods for Measuring Recovery

This study used an alternative method of analysis to determine the proportion of injured participants exhibiting abnormally low scores on measures of symptoms, balance, and cognitive functioning, during the first week following concussion. We addressed this goal through the use of SRB methods developed in studies of epilepsy surgery outcomes, which is a different approach than those previously employed in studies examining recovery following sports concussion (Barr & McCrea, 2001; Barr, 2003; Hinton-Bayre et al., 1999). While the SRB method may be more difficult to use than the RCI, it offers several advantages in the research setting by taking into account differences in test scores at baseline, as well as controlling for other factors, including practice effects and regression to the mean. The SRB method also offers the potential to more closely investigate the influence of additional demographic variables on test–retest outcomes, which then allows the inclusion of an empirically derived demographic correction in the standard regression.

Our use of the two-tailed 90% confidence interval for detection of impairment is rather conservative, providing a 5% chance of false positives (i.e., misclassifying a normal participant as impaired) for any single measure. When looking at the full battery of measures (e.g., GSC, SAC, BESS, and Neuropsychological Testing Battery), the expected false positive rate increased to 27.3%, conservatively assuming complete orthogonality. Our control group data used to determine impairment in the concussion group fell within the expected range of false positives in nearly all instances. In a clinical setting, a less conservative confidence interval may be preferred to maximize the sensitivity of injury detection

at the cost of some degree of specificity, especially when the primary interest is protecting young sports participants from the ill effects of recurrent concussion (Barr & McCrea, 2001).

Implications for Sports Concussion Management

Prospective, empirical data on the rate and trajectory of individual recovery not only advance our understanding of the natural history of concussion, but also have more direct clinical implications specific to the management of sport-related head injuries. Defining “recovery” following sports concussion on the basis of findings from serial neuropsychological and other standardized testing has been the subject of great debate. Our previously reported group data analyses delineated a *typical* slope of recovery from concussion (McCrea et al., 2003), but did not provide a methodology for clinical decision making on an individual case basis. The more advanced SRB methods employed in this study revealed a higher percentage of players with concussion to still be impaired 1 week after injury than that previously suggested by group recovery data analyses. These data from the current study indicate that on most measures “return to baseline” does not necessarily reflect full recovery. The use of statistical models that empirically identify meaningful change while controlling for baseline test performance and practice effects on serial testing is essential to classifying impairment due to any condition. Further refinement and simplification of this approach is likely necessary to provide the sports medicine clinician with a user-friendly method to *measure* a player’s level of recovery and readiness to return to play after concussion.

Relying primarily on a player’s self-reported symptom recovery to guide injury management and return to play decision making after sport-related concussion is problematic. The sensitivity of symptom assessment based on a player’s self-report is acceptable soon after injury, but diminishes after a few days. It is clear from the data on days 2 and 7, that even when players have experienced the resolution of symptoms as measured by the GSC, they may continue to exhibit deficits on objective measures of balance and cognitive functioning. A player’s potential motivation to under-report symptoms in hopes of a more rapid return to

play also complicates matters. Those injured players who reported being symptom free but continued to exhibit mild impairment on standardized testing and formal neuropsychological testing 1 week postinjury may be at increased risk of recurrent or more severe injury (Guskiewicz et al., 2003) if returned to play based solely on their reported symptoms without objective recovery data to guide the clinician's decision making. Future studies may consider including a formal measure of symptom minimization response bias, and this forum may provide an interesting laboratory for neuropsychologists to compare this form of response bias to that of symptom exaggeration or malingering often encountered in other clinical or forensic settings.

A multidimensional model of sports concussion assessment is supported by our findings. Postconcussive symptoms, cognitive dysfunction, and postural instability are all common sequelae of concussion, but may manifest differently across individuals. Multidimensional assessment of all domains affected by concussion yields the greatest sensitivity in detecting injury and the best method for assessing postinjury recovery. The combined battery of brief screening instruments (total administration time < 15 min) that measured postconcussive symptoms, cognitive functioning, and balance provided a sensitive and specific means to detect and characterize concussion during the acute post-injury period, particularly on the sports sideline immediately after concussion. The SAC and neuropsychological test battery yielded similar rates of impairment on day 2, but neuropsychological testing provided a more sensitive measure of subtle cognitive dysfunction further out from injury, characterized by mild residual deficits in delayed recall memory, cognitive processing speed, and verbal fluency. Based on our findings, the combination of brief screening instruments appropriate for emergent use on the sideline and more extensive neuropsychological testing to assess recovery may be most appropriate for clinical use.

Given the frequency of impaired postural stability in the current study, balance testing is considered an important part of any assessment model to identify neurological dysfunction following concussion in athletes. Balance deficits, like postconcussion symptoms and cognitive impairment, may manifest and recover differently across athletes. As in the case with cognitive testing, obtaining baseline testing on clinical balance measures such as the BESS provides the greatest clinical accuracy in identifying the residual effects of concussion.

Inclusion of the neuropsychological test data only minimally increased the sensitivity and reduced the specificity of the battery of brief instruments within the first 2 days after concussion, but the addition of neuropsychological testing more than doubled the sensitivity and slightly increased the specificity of the brief battery at day 7. The relative value of neuropsychological testing is demonstrated by its superior sensitivity in detecting subtle neurocognitive impairment further out from injury, especially in players otherwise reporting to be completely symptom free, although there are some methodological considerations which may complicate the interpretation of these data. These

data support the recommendation that neuropsychological testing be performed only when an injured participant reports being symptom free, which is also supported by practical and methodological considerations. Protocols that include neuropsychological testing at fixed intervals are appropriate for research intended to empirically track recovery, but are inappropriate in a clinical setting when a player is still symptomatic and should be withheld from competition regardless of the neuropsychological test results. Unnecessary serial testing, in addition to being burdensome to the athlete and medical staff, also introduces practice effects that may confound the interpretation of performance on subsequent testing (i.e., when a player reports being symptom free and is otherwise ready to return to play).

Study Limitations

It is possible that some players who sustained a concussion while enrolled in this study did not report their injury and were not identified by the team physician or certified athletic trainer. Recent reports (McCrea et al., 2004) suggest that the rate of concussion, even in well-controlled studies, is higher than that documented in the literature, due to a combination of players not recognizing the signs of injury or not reporting a concussion in order to continued uninterrupted sports participation.

The SRB method is subject to the reliability and validity of the main outcome measures used in this study, which have been supported by earlier studies on the effects of sports concussion. The availability of baseline data for injured and control participants on all concussion assessment measures also adds strength to the model by providing the most reliable means for detecting meaningful change in individual athletes. Although we incorporated most of the pencil-and-paper tests that have been routinely employed in sports concussion research, it is conceivable that a different test battery may have proven more or less sensitive to the lingering effects of concussion. There have as yet, however, been no direct comparisons of the sensitivity among pencil-and-paper or computer batteries being proposed for this purpose, and no conventional or computerized test battery has been established as the "gold standard".

The serial testing model employed in this study differs from previous SRB paradigms in epilepsy and cardiac surgery in the number of postevent testing sessions, particularly for the brief measures that were administered on several consecutive days after concussion. Further investigation is required to fully appreciate the effects of repeated neuropsychological testing, and the SRB approach at least provides one methodology to do so. It is possible, for instance, that the control group is more readily able to benefit from practice on some neurocognitive measures, and this practice effect is likely to be attenuated in concussed players who are still encephalopathic, especially during the acute postinjury phase. Therefore, the normative group may not really be an appropriate control group to use for this purpose in predicting performance for any time point beyond

the first postinjury test session because the controls are likely to benefit from practice effects to a significantly greater extent than players who are suffering from the acute effects of concussion at the time of testing. This is likely to result in overclassifying injured players as being “impaired” even though they may have completely recovered. This issue cannot be overlooked, particularly when interpreting the comparative rates of impairment for injured and control participants beyond the acute phase on postinjury day 7. Future studies should consider utilizing a controlled, randomized design to compare cognitive and balance recovery patterns for concussed symptomatic athletes with concussed asymptomatic athletes to validate the current findings, and to substantiate our recommendation that testing be conducted once an athlete is reporting to be symptom free. Unfortunately, participant attrition disallowed application of our analysis to look at the lengthier course of recovery 90 days after concussion. Future studies should implement tightly controlled mechanisms for tracking injured players beyond the completion of the sports season to allow analysis of longer term outcomes.

Conclusion

In summary, sport-related concussion is characterized by a combination of measurable symptoms, cognitive dysfunction, and postural instability that follows a gradual course of recovery over several days in most cases. Relying solely on a player’s self-reported recovery is not recommended, as a significant percentage of participants who report being completely symptom free after concussion may continue to show significant impairments on more sensitive standardized testing. Brief screening instruments are most sensitive and specific in accurately classifying injured and non-injured participants during the acute postinjury phase, while neuropsychological testing may be more sensitive to the subtle cognitive effects of concussion further out from injury, especially when a player otherwise reports being completely symptom free. Deferring neuropsychological testing until the injured player reports a full symptom recovery is recommended in a clinical setting, and for future studies investigating the incremental utility of neuropsychological testing in identifying the residual effects of sport-related concussion. Statistical models that empirically measure meaningful change on serial testing may provide a reliable benchmark for determining recovery and clinical decision making about an individual athlete’s readiness to return to competition after sport-related concussion. These data provide an empirical base to be considered by sports governing bodies and expert panels responsible for developing practice guidelines for clinical decision making on return to competition after sport-related concussion.

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BAILES EXHIBIT 9

Acute Effects and Recovery Time Following Concussion in Collegiate Football Players

The NCAA Concussion Study

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STUDIES IN BASIC NEUROSCIENCE have demonstrated that mild traumatic brain injury (concussion) is followed by a complex cascade of ionic, metabolic, and physiological events that can adversely affect cerebral function for several days to weeks.^{1,2} Concussive brain injuries trigger a pathophysiological sequence characterized earliest by an indiscriminate release of excitatory amino acids, massive ionic flux, and a brief period of hyperglycolysis, followed by persistent metabolic instability, mitochondrial dysfunction, diminished cerebral glucose metabolism, reduced cerebral blood flow, and altered neurotransmission. These events culminate in axonal injury and neuronal dysfunction.²⁻⁵ Clinically, concussion eventuates in neurological deficits, cognitive impairment, and somatic symptoms.⁶

Sport-related concussion is now widely recognized as a major public

See also pp 2549 and 2604 and Patient Page.

Context Lack of empirical data on recovery time following sport-related concussion hampers clinical decision making about return to play after injury.

Objective To prospectively measure immediate effects and natural recovery course relating to symptoms, cognitive functioning, and postural stability following sport-related concussion.

Design, Setting, and Participants Prospective cohort study of 1631 football players from 15 US colleges. All players underwent preseason baseline testing on concussion assessment measures in 1999, 2000, and 2001. Ninety-four players with concussion (based on American Academy of Neurology criteria) and 56 noninjured controls underwent assessment of symptoms, cognitive functioning, and postural stability immediately, 3 hours, and 1, 2, 3, 5, 7, and 90 days after injury.

Main Outcome Measures Scores on the Graded Symptom Checklist (GSC), Standardized Assessment of Concussion (SAC), Balance Error Scoring System (BESS), and a neuropsychological test battery.

Results No player with concussion was excluded from participation; 79 players with concussion (84%) completed the protocol through day 90. Players with concussion exhibited more severe symptoms (mean GSC score 20.93 [95% confidence interval {CI}, 15.65-26.21] points higher than that of controls), cognitive impairment (mean SAC score 2.94 [95% CI, 1.50-4.38] points lower than that of controls), and balance problems (mean BESS score 5.81 [95% CI, -0.67 to 12.30] points higher than that of controls) immediately after concussion. On average, symptoms gradually resolved by day 7 (GSC mean difference, 0.33; 95% CI, -1.41 to 2.06), cognitive functioning improved to baseline levels within 5 to 7 days (day 7 SAC mean difference, -0.03; 95% CI, -1.33 to 1.26), and balance deficits dissipated within 3 to 5 days after injury (day 5 BESS mean difference, -0.31; 95% CI, -3.02 to 2.40). Mild impairments in cognitive processing and verbal memory evident on neuropsychological testing 2 days after concussion resolved by day 7. There were no significant differences in symptoms or functional impairments in the concussion and control groups 90 days after concussion.

Conclusions Collegiate football players may require several days for recovery of symptoms, cognitive dysfunction, and postural instability after concussion. Further research is required to determine factors that predict variability in recovery time after concussion. Standardized measurement of postconcussive symptoms, cognitive functioning, and postural stability may enhance clinical management of athletes recovering from concussion.

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health concern in the United States and worldwide.^{3,7-9} Despite rule changes and advances in protective equipment, the incidence rate of concussion in contact

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and collision sports continues to be relatively high.¹⁰ Overall, concussion is one of the most common injuries in many collegiate sports.^{11,12} Recent data from the National Collegiate Athletic Association (NCAA) Injury Surveillance System reveal that concussion accounted for a significant percentage of total injuries among athletes participating in collegiate ice hockey (12.2%), football (8%), and soccer (4.8%) during the 2002-2003 season.¹¹

Of all sports, football has the highest absolute number of concussions each year because of the large volume of participants at the high school and collegiate levels.^{11,13,14} Recent epidemiological and prospective clinical studies estimate that approximately 3% to 8% of high school and collegiate football players sustain a concussion each season.^{10,13,15-25} More concerning is the trend toward an increasing rate of concussion in collegiate football over the last 7 years.^{11,12}

Despite a growing body of sport-related concussion research, little evidence-based guidance is available on how long it takes for an athlete to recover after concussion and when it is safe to return to competition. A review of the literature reflects estimates of symptom and cognitive recovery ranging anywhere from several hours to several weeks after sport-related concussion.^{15,18,19,21-24,26-36} Computerized and clinical tests have detected postural stability deficits at least 3 days after concussion,³⁷⁻⁴¹ but the course of longer-term recovery in balance functioning has not been extensively studied. It also remains unclear whether all domains affected by concussion (eg, symptoms, cognition, balance) follow the same or different recovery patterns.

Studying the course of recovery of postconcussive abnormalities is a critical step toward determining the interval during which a concussed brain may be most vulnerable to reinjury and establishing evidence-based guidelines for safe return to play by athletes after concussion.² The purpose of this NCAA-sponsored study was to prospectively measure the acute effects of concus-

sion and the continuous time course to recovery following concussion in competitive athletes participating in collegiate football.

METHODS

Participants

A total of 1631 football players from 15 NCAA Division I, II, and III member institutions were enrolled in 1 arm of a larger cohort study of the effects of sport-related concussion in the 1999, 2000, and 2001 seasons. In sum, 2410 player-seasons were analyzed; 779 players were enrolled for more than 1 year of the study. A case series of 94 players who sustained a concussion (5.76% of players; 3.90% of player-seasons) were enrolled in an extensive injury assessment protocol.

A noninjured control was selected from each injured player's team; 56 controls matched to injured players on age, years of education, and baseline performance on concussion assessment measures were administered the identical protocol during the first year of the study.

A master list of potential controls for each player was formed after preseason baseline testing, which facilitated immediate selection of a matched control in the event of a concussion during competition and allowed follow-up testing of control players under the same conditions and retest intervals as injured players. Limited resources did not allow enrollment of controls in years 2 and 3 of the study, which had a minimal effect on matching characteristics for the complete study sample. As a group, control participants were slightly younger and less educated than injured participants, but there were no statistically significant group differences in history of concussion or other neurological disorders (TABLE 1). There also were no significant differences in baseline performance on assessment measures for injured and control participants (Table 1), with the exception of the Trail-Making Test Part B.⁴²⁻⁴⁷

This study was approved by the institutional review boards for protection of human research subjects at the

Table 1. Concussion Group and Control Group Characteristics and Baseline Test Results

Characteristics	Concussion Group (n = 94)*	Control Group (n = 56)*	Mean Difference (95% CI)
Demographics			
Age, y	20.04 (1.36)	19.20 (1.45)	0.84 (0.37 to 1.32)
Academic year (collegiate)	2.78 (1.18)	2.02 (1.23)	0.76 (0.35 to 1.16)
Height, in	73.50 (2.94)	72.75 (3.23)	0.75 (−0.28 to 1.78)
Body weight, kg	105.87 (21.10)	98.33 (20.79)	7.54 (0.47 to 14.62)
Self-reported history			
No. of previous concussions in past 7 y	0.58 (0.78)	0.39 (0.68)	0.19 (−0.07 to 0.44)
Concussion (lifetime), No. (%)	41 (43.2)	17 (30.4)	12.8 (0.0 to 28.9)
ADHD, No. (%)	2 (2.30)	1 (1.80)	0.5 (0.0 to 59.2)
Learning disability, No. (%)	2 (2.30)	1 (1.80)	0.5 (0.0 to 58.8)
Baseline test results†			
GSC total score ¹⁷	1.95 (4.94)	0.99 (3.26)	0.96 (−0.49 to 2.43)
SAC total score ⁴²	27.40 (2.17)	27.43 (1.77)	−0.03 (−0.68 to 0.61)
BESS total score ⁴¹	11.89 (8.09)	12.73 (7.57)	−0.84 (−3.47 to 1.80)
HVLT Immediate Memory ⁴³	25.03 (4.36)	25.31 (4.05)	−0.28 (−1.70 to 1.13)
HVLT Delayed Recall ⁴³	8.61 (2.18)	9.15 (2.13)	−0.54 (−1.27 to 0.18)
HVLT Recognition ⁴³	22.60 (1.97)	22.94 (1.26)	−0.34 (−0.92 to 0.24)
Trail-Making Test Part B ⁴⁴	64.42 (22.22)	57.30 (18.69)	7.12 (0.12 to 14.11)
SDMT ⁴⁵	55.56 (11.61)	58.90 (12.19)	−3.34 (−7.29 to 0.60)
Stroop Color-Word Test ⁴⁶	47.21 (9.23)	48.66 (9.75)	−1.45 (−4.59 to 1.70)
COWAT ⁴⁷	40.46 (12.36)	37.15 (10.61)	3.31 (−0.61 to 7.23)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BESS, Balance Error Scoring System; CI, confidence interval; COWAT, Controlled Oral Word Association Test; GSC, Graded Symptom Checklist; HVLT, Hopkins Verbal Learning Test; SAC, Standardized Assessment of Concussion; SDMT, Symbol Digit Modalities Test.

*Data are expressed as mean (SD) unless otherwise specified.

†See Table 2 for explanation of total possible range of scores.

RECOVERY TIME AFTER CONCUSSION

host institutions of the principal investigators. All participants granted written informed consent prior to enrollment in the study.

Study Design

All participants underwent a preseason baseline evaluation on a battery of concussion assessment measures prior to their first year of participation in the study. An extensive health history questionnaire was also administered at baseline to generate a database of demographic information, concussion history, and preexisting neurological and other medical conditions.

Injured players were identified and enrolled in the study protocol by a team physician or certified athletic trainer present on the sideline during an athletic contest or practice. *Concussion* was defined as an injury resulting from a blow to the head causing an alteration in mental status and 1 or more of the following symptoms prescribed by the American Academy of Neurology Guideline for Management of Sports Concussion: headache, nausea, vomiting, dizziness/balance problems, fatigue, difficulty sleeping, drowsiness, sensitivity to light or noise, blurred vision, memory difficulty, and difficulty

concentrating.^{48,49} Criteria contributing to the identification of a player with a concussion also included the observed mechanism of injury (eg, acceleration or rotational forces applied to the head), symptoms reported or signs exhibited by the player, and reports by medical staff or other witnesses regarding the condition of the injured player. Loss of consciousness, posttraumatic amnesia (eg, inability to recall exiting the field, aspects of the examination), and retrograde amnesia (eg, inability to recall aspects of the play, events prior to injury, score of the game) were documented immediately after injury.

All players identified by the team physician or certified athletic trainer as having a concussion according to the study's injury definition and criteria were tested with a Graded Symptom Checklist (GSC),¹⁷ the Standardized Assessment of Concussion (SAC),⁴² and the Balance Error Scoring System (BESS)⁴¹ on the sideline immediately following injury. Follow-up testing on these measures was then conducted 2 to 3 hours after injury (postgame/postpractice) and again on postinjury days 1, 2, 3, 5, 7, and 90. A brief neuropsychological test battery was administered to assess neurocognitive functioning at baseline and on

postinjury days 2, 7, and 90. Because research data were collected in the context of direct clinical care delivery, examiners were not blinded to the players' group assignments (injured vs control) at the time of evaluation. Assessments were conducted by certified athletic trainers who were trained by the researchers on administration and scoring of all outcome measures used in the study.

Main Outcome Measures

TABLE 2 summarizes the measures used in this study to assess postconcussive symptoms, cognitive functioning, and postural stability. All of these measures have been used extensively in head injury research, including studies on the effects of sport-related concussion. Several reports have demonstrated the reliability and accuracy of the GSC,³⁶ SAC,^{20,22} BESS,³⁹⁻⁴¹ and components of the neuropsychological test battery¹⁹ in correctly classifying persons with and without concussion. Clinicians also recorded information on injury mechanism, severity, management, recovery, and return to play.

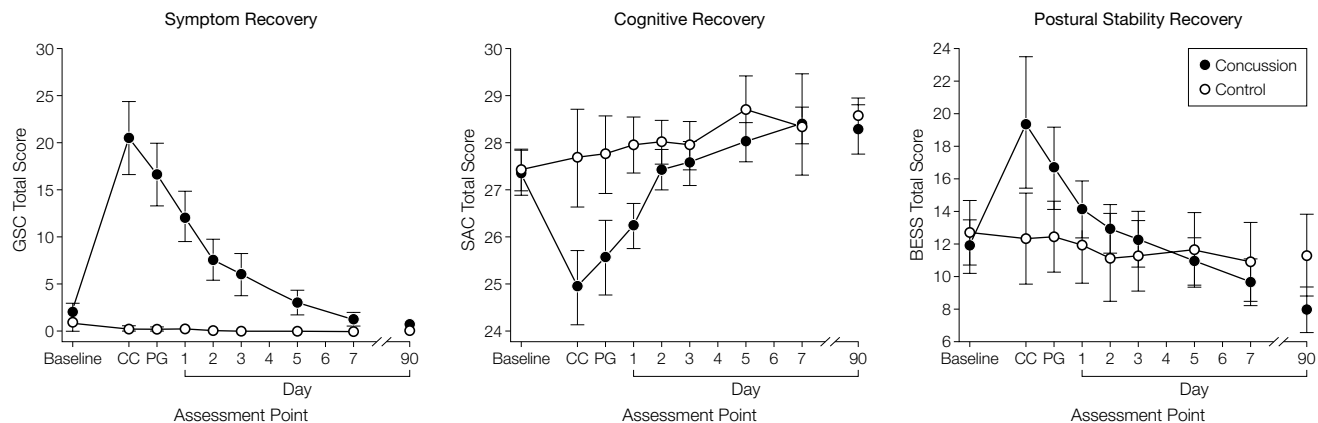
Statistical Analysis

We initially graphed the recovery curves for symptoms, cognition, and balance

Table 2. Main Outcome Measure Characteristics

Measure	Functional Domain	Description	Score Range	Time Needed to Administer
Graded Symptom Checklist ¹⁷	Postconcussive symptoms	Self-rated presence and severity of 17 symptoms (eg, headache, dizziness)	Likert scale of 0 (no symptoms) to 6 (severe) per item; total score range, 0-102; higher score indicates more severe symptoms	2-3 min
Standardized Assessment of Concussion ^{42*}	Cognitive functioning (orientation, immediate and delayed memory, concentration) Neurological screening (strength, sensation, coordination)	Brief neurocognitive assessment and neurological screening; documentation of loss of consciousness, posttraumatic amnesia, retrograde amnesia	Total score range, 0-30; lower score indicates more severe cognitive impairment	5 min
Balance Error Scoring System ⁴¹	Postural stability	Noninstrumented, clinical assessment of postural stability in double-leg, single-leg, and tandem stances on firm and foam surfaces	No defined range; test score equals total number of errors committed by test taker; higher score indicates more severe postural instability	5 min
Neuropsychological test battery ^{43-47*}	Cognitive functioning (attention, concentration, processing speed, mental flexibility, anterograde memory, verbal fluency)	Hopkins Verbal Learning Test (memory) ⁴³ ; Trail-Making Test Part B (cognitive processing) ⁴⁴ ; Symbol Digit Modalities Test (cognitive processing) ⁴⁵ ; Stroop Color-Word Test (mental flexibility) ⁴⁶ ; Controlled Oral Word Association Test (verbal fluency) ⁴⁷	Total score range based on individual measures; lower score indicates more severe impairment except for Trail-Making Test (total time to complete)	25 min

*Alternate forms were used to minimize practice effects from repeat testing on the Standardized Assessment of Concussion and the neuropsychological test battery.

Figure. Symptom, Cognitive, and Postural Stability Recovery in Concussion and Control Participants

Higher scores on the Graded Symptom Checklist (GSC) indicate more severe symptoms; lower scores on the Standardized Assessment of Concussion (SAC) indicate poorer cognitive performance; and higher scores on the Balance Error Scoring System (BESS) indicate poorer postural stability. Error bars indicate 95% confidence intervals. CC indicates time of concussion; PG, postgame/postpractice. On the BESS, multiple imputation was used to estimate means and 95% confidence intervals for control participants for the CC and PG assessments.

across all time points, with 95% confidence intervals. We also fit multivariate regression models to further explore recovery effects and control for potential confounders. Because the data involved longitudinal observations on a set of injured athletes, we fit generalized estimating equation models, with an identity link function, assumed Gaussian residual variation, and independent working correlation matrix.^{50,51} We used this model to estimate the mean differences in test scores on each of the main outcome measures between injured players and uninjured controls at each time point. In all analyses, we controlled for baseline scores on the respective tests, history of concussion, and institution. In addition, we controlled for academic year and any self-reported history of a learning disability or attention-deficit/hyperactivity disorder in cognitive and neuropsychological models and for body mass index and height in balance models.

The data collection protocol was time-sensitive; because of clinical workload and logistical constraints, testing could not always be performed at the specified time points, particularly at the time of concussion and at the postgame/postpractice time point. Across all time points for all participants, 86% of data were complete. To examine the poten-

tial effect of missing data on the modeling results, we compared the baseline scores for the missing and nonmissing player data at every time point for all outcomes. The baseline scores did not differ between players with missing and nonmissing data, suggesting that the data were missing at random, as described in Diggle et al.⁵² We also estimated the missing data using a single imputation model, based on time and player status (injured vs control) and obtained essentially identical results on reanalysis of the imputed data. The sole exception was for data for controls on the BESS balance test at the time of concussion and at the postgame/postpractice time point; baseline scores differed between missing and nonmissing data for this measure at these 2 time points, creating bias in the observed change-from-baseline effect. To overcome this problem, we used multiple imputation to estimate the control means and confidence intervals only for these 2 time points. No imputation was used in any of the generalized estimating equation regression models, since these controlled for baseline test scores. Data were analyzed with SPSS software, version 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

Ninety-four players who had a concussion during a football practice (56.8% of

concussions studied) or game were studied. Most injuries were classified as either grade 1 or grade 2 concussions according to the Cantu⁵³ (98.6%), Colorado⁵⁴ (93.3%), and American Academy of Neurology⁴⁸ (93.2%) sports-concussion grading scales based on our post hoc review of injury characteristics. A small number of injured players experienced loss of consciousness (6.4%; median duration, 30 seconds) or exhibited posttraumatic amnesia (19.1%; median duration, 90 minutes) or retrograde amnesia (7.4%; median duration, 120 minutes). There was no loss of consciousness, posttraumatic amnesia, or retrograde amnesia associated with 77.8% of injuries. Eleven players exhibited delayed onset of symptoms after concussion (mean [SD] delay, 14.4 [15.5] minutes) and therefore were not evaluated immediately after concussion. No player who sustained a concussion refused to participate or was excluded from the study protocol, but information on unidentified or unreported concussions was not available. Four players had more than 1 concussion during a season. Seventy-nine players with concussion (84%) completed the assessment protocol through the day 90 assessment.

The recovery curves shown in the FIGURE depict the symptoms, cognitive functioning, and postural stabil-

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ity of injured players vs controls across all assessment points. The shape of these curves illustrates a pattern of more severe symptoms, cognitive impairment, and balance problems (postural instability) immediately after injury, followed by a gradual improvement over the first several postinjury days.

After controlling for potential confounders in the multivariate regression models, the recovery patterns depicted in the Figure persist. TABLE 3 provides adjusted mean differences and 95% confidence intervals for the concussion vs

control groups, controlling for covariates, on measures of symptoms, cognitive functioning, and balance at each postinjury assessment point. Increased symptoms were very evident during the acute phase immediately following concussion, and strong group differences in symptom scores persisted through postinjury day 5. On average, symptoms in players with concussion resolved by day 7. Ninety-one percent of players with concussion returned to personal baseline symptom levels within 7 days after concussion.

Cognitive impairment in players with concussion was most severe at the time of injury and persisted through postinjury day 2. Milder cognitive deficits appeared to persist up to postinjury day 5 but, on average, resolved by day 7. Balance deficits were most pronounced during the first 24 hours after concussion but appeared to resolve by day 5, slightly earlier than symptoms and cognitive effects resolved.

After plotting raw means for the concussion and control groups on the neuropsychological tests, we fit multivariate regression models to further explore these effects and to control for variations in baseline scores on each test and other potential confounders. TABLE 4 presents raw group means and 95% confidence intervals for the concussion and control groups, and TABLE 5 provides adjusted mean differences and 95% confidence intervals, controlling for covariates, on the neuropsychological test battery at postinjury days 2, 7, and 90. Players with concussion exhibited mild impairment in cognitive processing speed and verbal fluency 2 days and 7 days after concussion. There was also suggestion of a subtle decline from baseline in players with concussion on measures of verbal memory and mental flexibility on postinjury day 2. On day 90, players with concussion performed less well than controls on a

Table 3. Model-Based Adjusted Estimates of Mean Differences Between Concussion and Control Groups in Symptoms, Cognitive Functioning, and Postural Stability*

Assessment Point	Mean Difference (95% Confidence Interval)		
	Symptoms (GSC)	Cognitive Functioning (SAC)	Postural Stability (BESS)
Time of concussion	20.93 (15.65 to 26.21)	-2.94 (-4.38 to -1.50)	5.81 (-0.67 to 12.30)
Postgame/postpractice	16.97 (12.61 to 21.33)	-2.15 (-3.26 to -1.04)	5.66 (1.27 to 10.06)
Postinjury day			
1	11.53 (8.37 to 14.69)	-1.59 (-2.43 to -0.75)	2.72 (-0.14 to 5.57)
2	6.88 (4.17 to 9.59)	-0.72 (-1.51 to 0.08)	2.33 (-0.30 to 4.95)
3	5.08 (2.27 to 7.88)	-0.46 (-1.25 to 0.32)	1.46 (-1.22 to 4.14)
5	2.02 (-0.03 to 4.06)	-0.52 (-1.28 to 0.25)	-0.31 (-3.02 to 2.40)
7	0.33 (-1.41 to 2.06)	-0.03 (-1.33 to 1.26)	-0.55 (-3.19 to 2.09)
90	0.62 (-0.90 to 2.14)	-0.51 (-1.41 to 0.39)	-2.45 (-5.09 to 0.18)

Abbreviations: BESS, Balance Error Scoring System; GSC, Graded Symptom Checklist; SAC, Standardized Assessment of Concussion.

*Estimated mean differences for the GSC are adjusted for baseline GSC score and number of previous concussions; SAC estimates are adjusted for baseline SAC score, academic year, number of previous concussions, history of learning disability and attention-deficit/hyperactivity disorder, and institution; BESS estimates are adjusted for baseline BESS score, height, body weight, number of previous concussions, and institution. Positive mean differences indicate more severe symptoms reported on the GSC and poorer performance on the BESS in the concussion group relative to baseline; negative mean differences indicate poorer performance in the concussion group on the SAC relative to baseline.

Table 4. Neuropsychological Test Battery Results in Concussion and Control Groups at Postinjury Days 2, 7, and 90*

Measure	Mean Score (95% Confidence Interval)					
	Day 2		Day 7		Day 90	
	Concussion Group	Control Group	Concussion Group	Control Group	Concussion Group	Control Group
Memory						
HVLT Immediate Memory ⁴³	24.41 (23.49-25.34)	25.29 (24.02-26.55)	25.63 (24.74-26.53)	25.85 (24.53-27.17)	26.25 (25.27-27.23)	27.61 (26.15-29.08)
HVLT Delayed Recall ⁴³	8.07 (7.52-8.61)	8.76 (8.04-9.47)	8.50 (7.94-9.06)	10.22 (8.37-12.06)	9.03 (8.49-9.56)	9.68 (8.97-10.39)
HVLT Recognition ⁴³	22.18 (21.80-22.57)	22.84 (22.39-23.28)	22.50 (22.18-22.82)	22.65 (21.91-23.39)	23.19 (22.92-23.46)	23.29 (22.94-23.64)
Cognitive processing						
Trail-Making Test Part B ⁴⁴	59.99 (55.65-64.32)	53.31 (48.62-58.00)	53.72 (49.44-58.00)	44.87 (40.51-49.24)	51.59 (47.62-55.57)	45.44 (41.10-49.78)
SDMT ⁴⁵	54.78 (52.50-57.06)	60.67 (57.09-64.24)	54.84 (52.69-57.00)	59.20 (55.93-62.46)	59.87 (57.42-62.31)	61.42 (57.30-65.54)
Mental flexibility						
Stroop Color-Word Test ⁴⁶	48.20 (45.83-50.56)	51.43 (48.73-54.13)	53.47 (51.16-55.78)	55.39 (52.16-58.62)	53.97 (51.65-56.30)	54.32 (50.27-58.37)
Verbal fluency						
COWAT ⁴⁷	39.99 (37.75-42.23)	40.29 (37.34-43.23)	41.57 (39.26-43.88)	42.63 (39.56-45.70)	42.65 (40.29-45.01)	44.94 (41.26-48.61)

Abbreviations: COWAT, Controlled Oral Word Association Test; HVLT, Hopkins Verbal Learning Test; SDMT, Symbol Digit Modalities Test.

*Higher scores on the Trail-Making Test indicate slower performance; lower scores indicate poorer performance on all other measures.

single measure of verbal fluency, but there were no lingering impairments in the concussion group on the other outcome measures.

COMMENT

The findings from this 3-year study indicate that collegiate football players require several days to recover after sport-related concussion. Injured athletes exhibited the most severe symptoms, cognitive dysfunction, and balance problems during the acute phase immediately after concussion, followed by a gradual course of recovery over 5 to 7 days. On average, cognitive functioning returned to normal within 5 to 7 days after concussion, but athletes required a full 7 days for postconcussive symptoms to completely return to baseline and control levels. Players with concussion exhibited a mild decline from baseline and control levels on neuropsychological measures of cognitive processing speed, new learning and memory, and mental flexibility 2 days after concussion; these measures returned to baseline levels by postinjury day 7. Balance testing also returned to normal within 3 to 5 days after concussion. There was no evidence of lingering symptoms, cognitive impairment, or balance problems in the concussion group at postinjury day 90. It is important to note that the rate of recovery after concussion varied from player to player in our study. These findings suggest that clinicians cannot necessarily expect that all collegiate football players will reach a complete recovery within 7 days after a concussion, as approximately 10% of players in this study required more than a week for symptoms to fully resolve. Furthermore, not all players demonstrated the same pattern of recovery in symptoms, cognition, and balance.

Concussion Threshold and Natural Recovery Course

While there is no single biological marker of concussion, data from this study demonstrate a threshold of acute impairments signifying the mildest form of traumatic brain injury. There was

Table 5. Model-based Adjusted Estimates of Mean Differences Between Concussion and Control Groups on the Neuropsychological Test Battery*

Measure	Mean Difference (95% Confidence Interval)		
	Day 2	Day 7	Day 90
Memory			
HVLT Immediate Memory ⁴³	-1.02 (-2.84 to 0.81)	-0.57 (-2.38 to 1.23)	-1.22 (-3.32 to 0.88)
HVLT Delayed Recall ⁴³	-0.59 (-1.62 to 0.44)	-1.63 (-3.62 to 0.35)	-0.02 (-1.04 to 1.00)
HVLT Recognition ⁴³	-0.50 (-1.24 to 0.24)	0.03 (-0.97 to 1.03)	0.16 (-0.58 to 0.91)
Cognitive processing			
Trail-Making Test Part B ⁴⁴	2.25 (-5.38 to 9.88)	4.10 (-3.53 to 11.73)	3.61 (-5.41 to 12.63)
SDMT ⁴⁵	-4.99 (-9.88 to -0.11)	-4.03 (-9.29 to 1.24)	0.25 (-4.94 to 5.43)
Mental flexibility			
Stroop Color-Word Test ⁴⁶	-2.00 (-5.66 to 1.66)	-0.98 (-4.56 to 2.60)	-0.80 (-4.54 to 2.95)
Verbal fluency			
COWAT ⁴⁷	-3.65 (-6.78 to -0.52)	-4.57 (-8.02 to -1.11)	-5.31 (-9.11 to -1.52)

Abbreviations: COWAT, Controlled Oral Word Association Test; HVLT, Hopkins Verbal Learning Test; SDMT, Symbol Digit Modalities Test.

*Estimates are adjusted for baseline scores on each respective measure, academic year, number of previous concussions, history of learning disability/attention-deficit/hyperactivity disorder, and institution.

clear and consistent evidence of cerebral dysfunction in cases of concussion without classic indicators of mild traumatic brain injury, such as loss of consciousness and posttraumatic amnesia. These data support a movement in the neurosciences toward a revised definition of concussion that emphasizes an *alteration* (as opposed to a loss) of consciousness or mental status as the hallmark of concussion and stresses the potential seriousness of all head injuries, even what has historically been referred to as a simple “ding.” Sports medicine professionals especially should be aware that the diagnosis of concussion does not require loss of consciousness, significant amnesia, or other focal neurological abnormalities associated with more severe head injury.

Animal studies have demonstrated a cascade of physiological events that adversely affect cerebral functioning for a period of days to weeks after a concussion.^{55,56} The pattern of impairment exhibited by injured players in our study of collegiate athletes provides indirect evidence of the same phenomena in humans through detailed testing of cognitive functioning, postural stability, and subjective symptoms at serial time points following concussion. Injured athletes exhibited significantly increased symptoms and functional impairments during the acute postconcussive phase that gradually re-

solved along the same neurophysiological course described in animal concussion models.² This appears to be the first prospective human study to include preinjury cognitive and motor baseline testing and to plot continuous recovery curves from a point immediately after concussion to several months after injury in a sizable group of persons with concussion.

Our findings contribute to the existing literature on the acute effects of and recovery from sport-related concussion. Interpretation of recovery data from earlier clinical studies has been hampered by varied definitions of concussion, limited follow-up assessment of injured players widely distributed over time, small sample sizes, lack of control groups, and failure to address all domains of postconcussive recovery (eg, neurological, symptomatic, cognitive, postural stability). Few studies have measured symptoms and functional impairments within minutes of injury to establish an early benchmark against which to track recovery.^{16,18,23,27} Several studies have reported that a portion of injured participants still exhibited cognitive impairment or postconcussive symptoms at the final assessment point used in the study, precluding any more precise determination of a recovery end point.^{26-28,33-36} It has also been unclear from earlier studies whether all do-

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mains affected by concussion follow similar or different recovery courses.

Implications for Sports Concussion Management

Despite recent advances in the science of sports concussion and attempts to reach expert consensus, there remains significant debate over which factors (eg, unconsciousness, amnesia, symptom duration) are most critical in determining concussion severity, expected recovery course, and how long a player should be withheld from competition after injury. Currently, sports concussion grading systems drive injury management strategies, but grading concussion severity is a difficult matter, even with the benefit of extensive standardized assessment data collected within minutes after injury. Grading injury severity assists in acute medical management of concussion but may not independently predict course of recovery or the best plan for safe return to play after injury. Therefore, perhaps less emphasis should be placed on grading concussion, with more emphasis on a standardized approach to measuring recovery in determining when it is safe for an athlete to return to competition. Based on our findings, the use of standardized assessment tools may assist clinicians in determining an athlete's level of recovery and readiness for safe return to competition after a concussion. Further study is required, however, to determine whether the use of these instruments significantly enhances injury management strategies and ultimately reduces the risks associated with sport-related concussion.

Injury surveillance studies have reported that the average length of time players are withheld from competition after concussion in high school and collegiate football ranges from 3 to 8 days, depending on the grade of injury severity.^{10,13} We previously found that the largest percentage of collegiate football players were withheld from competition for an average of less than 5 days after concussion.²⁵ The disparity between our data on average recovery time and concurrent reports on

time withheld from play after concussion raises concerns based on the common assumption that resuming competition before reaching full recovery may increase the risks of recurrent injury, cumulative impairment, or even catastrophic outcome. Additional data are required to more precisely determine the risks associated with further injury exposure before reaching a complete recovery after concussion.

Study Limitations

Several limitations to our study warrant consideration. First, most of the concussions studied were of mild to moderate severity. Further study is under way to explore how acute injury severity affects the trajectory and time course of recovery. It is also possible that some players who may have had a concussion during the study were not identified. Whether as part of a research study or in general clinical practice, it has long been thought that the rate of concussion is likely underestimated because of the reluctance of some athletes to report injury or their inability to recognize the signs of injury.⁵⁷ Our study is not exempt from this form of potential selection bias in the sample of injured players studied. These data are also subject to the reliability and validity of the main outcome measures we used, which are supported by earlier studies on the accuracy of these measures in detecting the effects of concussion in athletes.^{19,20,22,36,39-41} Obtaining a preinjury baseline for all players on these measures provides the most sensitive means to detect reliable change in performance attributable to concussion and track postinjury recovery.²⁰ Still, our main outcome measures provide indirect evidence of concussion through assessment of symptoms and functional deficits, not cerebral activity directly, and are prone to some degree of error common to all forms of clinical measurement.

While we have attempted to control for potential confounding of postinjury test results by noninjury factors (eg, education, baseline test performance, test practice effects, history of concussion, examiner), we also recognize that further study is required to conclude to what

extent injury (eg, unconsciousness, amnesia, previous history of concussion) and noninjury factors may affect recovery time for athletes at all competitive levels. Because our study sample was limited to collegiate athletes, it is unclear if these data can be applied to the expected course of recovery by younger (eg, high school) or older (eg, professional) athletes with a concussion. Concurrent research, however, illustrates a similar pattern of postconcussive recovery in symptoms, cognition, and balance by high school football players.⁵⁸ We are also investigating to what extent these data can be generalized to recovery after concussion from other sources of trauma (eg, motor vehicle crashes).

CONCLUSION

Objective data from this study illustrate the natural course of recovery by collegiate football players over a period of several days following concussion and contribute to a shift in the direction of evidence-based guidelines for determining the best time course for young athletes to return to play after injury. These findings also set the stage for randomized research trials to determine the most effective methods for clinical management of athletes recovering from concussion. Further study is necessary to elucidate factors that predict recovery across all functional domains affected by concussion and to determine the recommended duration of a symptom-free waiting period to minimize the risks associated with recurrent concussion or other adverse outcomes resulting from sport-related head injuries.

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Author Contributions: As principal investigator, Dr McCrea had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McCrea, Guskiewicz, Randolph, Kelly.

Acquisition of data: McCrea, Guskiewicz, Marshall, Onate.

Analysis and interpretation of data: McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Yang, Kelly.

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BAILES

EXHIBIT 10

Incidence, Clinical Course, and Predictors of Prolonged Recovery Time Following Sport-Related Concussion in High School and College Athletes

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Abstract

Sport-related concussion (SRC) is typically followed by clinical recovery within days, but reports of prolonged symptoms are common. We investigated the incidence of prolonged recovery in a large cohort ($n = 18,531$) of athlete seasons over a 10-year period. A total of 570 athletes with concussion (3.1%) and 166 controls who underwent pre-injury baseline assessments of symptoms, neurocognitive functioning and balance were re-assessed immediately, 3 hr, and 1, 2, 3, 5, 7, and 45 or 90 days after concussion. Concussed athletes were stratified into typical (within 7 days) or prolonged (> 7 days) recovery groups based on symptom recovery time. Ten percent of athletes ($n = 57$) had a prolonged symptom recovery, which was also associated with lengthier recovery on neurocognitive testing ($p < .001$). At 45–90 days post-injury, the prolonged recovery group reported elevated symptoms, without deficits on cognitive or balance testing. Prolonged recovery was associated with unconsciousness [odds ratio (OR), 4.15; 95% confidence interval (CI) 2.12–8.15], posttraumatic amnesia (OR, 1.81; 95% CI, 1.00–3.28), and more severe acute symptoms ($p < .0001$). These results suggest that a small percentage of athletes may experience symptoms and functional impairments beyond the typical window of recovery after SRC, and that prolonged recovery is associated with acute indicators of more severe injury. (*JINS*, 2013, *19*, 22–33)

Keywords: Brain injury, Concussion, Neuropsychological tests, Sport injuries, Neurological disorders, Closed head injury

INTRODUCTION

Based on its reported prevalence, acute effects, and fears over potential long-term neurological consequences, sport-related concussion has become the focus of increasing concern from clinicians, researchers, sporting organizations, and athletes themselves over the last 2 decades (DeKosky, Ikonomic, & Gandy, 2010; Kelly, 1999; Langlois, Rutland-Brown, & Wald, 2006; McCrory et al., 2005, 2009; “Nonfatal traumatic

brain injuries from sports and recreation activities—United States, 2001–2005,” 2007). Concussion is a frequent injury in contact and collision sports (e.g., football, hockey, wrestling) at all levels of participation, including youth sports (Guskiewicz, Weaver, Padua, & Garrett, 2000; Halstead & Walter, 2010; Powell & Barber-Foss, 1999). A recent study indicated that from 1997 to 2007 emergency department visits for 8- to 13-year-old children affected by concussion in organized team sports have doubled, and had increased by more than 200% in the 14- to 19-year-old group (Bakhos, Lockhart, Myers, & Linakis, 2010).

Extensive research over the last decade has significantly advanced our scientific understanding of the true natural

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history of clinical recovery following sport-related concussion. In general, the findings on acute recovery have been favorable. A 2003 report was the first to plot the continuous time course of acute recovery within several days after concussion, indicating that more than 90% of athletes reported a symptom recovery within 1 week (McCrea et al., 2003, 2005). Several other prospective studies have since consistently demonstrated that the overwhelming majority of athletes achieve a complete recovery in symptoms, cognitive functioning, postural stability, and other functional impairments over a period of approximately one to two weeks following concussion (Belanger & Vanderploeg, 2005; Broglio & Puetz, 2008; Collins et al., 1999; Guskiewicz et al., 2003; Macciocchi, Barth, Alves, Rimel, & Jane, 1996).

There are frequent anecdotal reports, however, of athletes who remain symptomatic or impaired on functional testing well beyond the window of recovery commonly reported in group studies. The greatest challenge arguably still facing sports medicine clinicians and public health experts is how to most effectively manage and reduce risk in this subset of athletes who do not follow the “typical” course of recovery. The precise frequency of athletes who do not follow the typical course of rapid, spontaneous recovery and instead exhibit prolonged postconcussive symptoms or other functional impairments after concussion remains unclear. While several studies have reported that the largest percentage of athletes achieve a complete recovery within one to two weeks (Belanger & Vanderploeg, 2005; Broglio & Puetz, 2008), limited research has suggested a lengthier recovery time in younger athletes (Field, Collins, Lovell, & Maroon, 2003), citing that roughly half of all high school athletes required more than 14 days to recover (Lau, Lovell, Collins, & Pardini, 2009; Lau, Collins, & Lovell, 2012). Unfortunately, these studies did not include controls, and applied criteria for “recovery” that may have resulted in high false positive rates due to criterion contamination that significantly complicate the interpretation of data from those studies. Furthermore, there is little empirical evidence on what risk factors may be associated with prolonged recovery time or poor outcome and how these risks can be modified in a clinical setting. A recent study of Australian Rules football players indicated that delayed return to sport after concussion was associated with acute symptom severity, but that study did not involve longitudinal tracking of concussed athletes beyond 7 days post-injury (Makdissi et al., 2010).

The current study used a longitudinal design to prospectively investigate the incidence, clinical course, and prediction of prolonged recovery time following sport-related concussion in a large sample of high school and collegiate athletes.

METHODS

Participants

This study combined datasets from three parallel, multi-center, prospective studies investigating the effects of sport-related concussion between 1999 through 2008. In total, 18,531 player seasons (i.e., total sport seasons of participation by all athletes)

were under surveillance during that 10-year period. Athletes who participated more than one year in the study had multiple sport seasons in the database. A cohort of 570 high school and collegiate athletes (3.1% of athlete seasons) who sustained a sport-related concussion in an organized team sport during this prospective research study was extensively studied. The injured cohort was 88.9 percent male and 11.1 percent female; 60.5% of injuries studied were at the high school participation level and 39.5% involved collegiate athletes. The distribution of concussions across sports was as follows: American football (80.7%), followed by soccer (13.3%), lacrosse (5.2%), and ice hockey (0.8%).

A control group ($n = 166$) of non-concussed athletes matched to the concussion group on demographic variables (i.e., sport, age, gender, years of education, level of competition) and baseline performance on the study’s main outcome measures was administered the same assessment protocol as the concussed group. The method for control group sampling and matching used in this study has been demonstrated to be effective in closely matching control subjects to concussed subjects and controlling for non-injury variables in our prior studies of high school and college athletes (Guskiewicz et al., 2003; McCrea, 2001; McCrea et al., 2003, 2005). The control group was 63.3% ($n = 105$) high school athletes and 36.7% collegiate athletes ($n = 61$). Limited resources did not allow us to enroll a control group of 570 athletes, but the current control group was of sufficient size to allow adequate matching and ample statistical power.

This study was approved by the institutional review board for protection of human research participants at the host institution of the principal investigators (Drs. Guskiewicz and McCrea). Written informed consent was obtained from all participants or their parent/guardian before participation in the study.

Study Design and Procedures

All athletes underwent a preseason baseline evaluation on a battery of concussion assessment measures upon enrollment in the study. Injured subjects were identified and enrolled in the study protocol by a team physician or certified athletic trainer present on the sideline using the same procedures to identify concussed athletes during an athletic contest or practice. Throughout the entire study, *concussion* was defined according to the American Academy of Neurology Guideline for Management of Sports Concussion (i.e., “a trauma-induced alteration in mental status that may or may not involve loss of consciousness”), which was the most widely accepted definition in the clinical and scientific communities at the time this study was initiated [Kelly & Rosenberg, 1997; “Practice parameter: the management of concussion in sports (summary statement) report of the Quality Standards Subcommittee,” 1997]. All athletes were closely monitored by medical staff over the course of their recovery.

Athletes were evaluated using the study’s standardized outcome measures on the sideline immediately following injury, 2–3 hr later, and again at several time points during the

first week post-injury. More extensive neuropsychological testing was administered 1–2 days and 1 week post-injury. All measures were then re-administered 45 days or 90 days post-injury. Over the 10-year study period, this assessment point of remote recovery moved from 90 to 45 days.

Main Outcome Measures

The Graded Symptom Checklist (GSC), Balance Error Scoring System (BESS), Standardized Assessment of Concussion (SAC), and a brief neuropsychological test battery were used to assess post-concussive symptoms, postural stability, and cognitive functioning, respectively. The GSC required athletes to rate the presence and severity of 25 common concussion symptoms on a 0–6 (6 most severe) Likert scale. The SAC is a brief cognitive screening tool that assesses orientation, concentration, and immediate and delayed memory. The BESS is a brief clinical measure of postural stability. Total scores on the GSC (range, 0–150), SAC (range, 0–30), and BESS (range, 0–60) were used for analysis. The traditional (i.e., “paper and pencil”) neuropsychological test battery used in this study included the Hopkins Verbal Learning Test (HVLT), Trail Making Test (Part B), Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), and Stroop Color-Word Test. Several studies on the effects of sport-related concussion have demonstrated the reliability and validity of the GSC, SAC, BESS and selected neuropsychological tests in assessing the effects of sport-related concussion (Barr & McCrea, 2001; Collins et al., 1999; Guskiewicz, 2003; Lovell et al., 2003; McCrea, 2001; McCrea et al., 2003, 2005). The tests included in the neuropsychological test battery were commonly used in sports concussion studies and clinical programs during the early years of our study period and were retained throughout our study to maximize consistency of our main outcome measures.

All measures were administered by study personnel (e.g., certified athletic trainers, research assistants, neuropsychologists) fully trained and supervised by the investigators on standardized assessment methods. Alternate forms of all cognitive outcome measures except the Stroop were used to reduce practice effects over repeated administrations. The order of test administration was the same for all injured and control subjects. This conventional battery was implemented at the outset of our studies, before the proliferation of computerized test batteries, and maintained throughout our studies.

Statistical Analysis

For our current analyses directly relevant to the study’s specific aims, injured players were stratified to one of two groups based on the following empirically-derived criteria:

Typical recovery group

Athletes were assigned to the typical recovery group if the change in their total score on the Graded Symptom Checklist (GSC) from pre-injury baseline to Day 7 post-injury was

inside the 95th percentile of the change score for the normal control group over the same period. Specifically, 94.7% of controls had a change of ≤ 5 points from baseline to day 7 on the GSC, so injured players were assigned to the typical recovery group if their change score from baseline to day 7 on the GSC was ≤ 5 . The 95th percentile was applied based on the recognition that there is a small degree of variability in GSC score even among normal, non-concussed athletes. The day 7 time point was used because of consistent reports in the literature indicating that athletes typically achieve a complete recovery within one week after concussion. Applying the 95th percentile to the definition of recovery also suggests that 5% of normal control group would not meet the criterion of “typical recovery” (i.e., representing a 5% “false positive” rate). It was believed that this definition was sufficiently conservative to define “typical recovery” based on GSC score, while also allowing for the normal psychometric variability of the scale. We specifically elected to use symptom recovery time (as quantified by GSC score relative to individual pre-injury baseline, controlling for normal variability on the scale) to stratify between typical vs. prolonged recovery because we were interested in the indicator relied on most in the setting of clinicians determining an athlete’s overall clinical recovery and fitness to return to play.

Prolonged recovery group

Conversely, injured players were assigned to the prolonged recovery group if their change score on the GSC from baseline to Day 7 was 6 or higher.

Our statistical analysis compared the typical recovery, prolonged recovery and control groups on several metrics relevant to the study’s specific aims. Since serial observations on individuals were collected over the study period, mixed models with interaction between time and group were performed to study differences among the three groups at each time point in symptom recovery, cognitive recovery, postural stability recovery, and neuropsychological recovery [1]. The unstructured covariance structure was used in the mixed model since it showed the lowest Akaike information criterion (AIC) among compound symmetric, autoregressive order one, and unstructured covariance structures.

For symptom, cognitive, and postural stability recovery, nine assessment time points were included: pre-injury baseline, time of concussion, 3 hr, and days 1, 2, 3, 5, 7, and 45/90 post-injury. Four time points (baseline, day 1–2, day 6–7, and day 45–90) were observed for neuropsychological recovery. As noted, the final assessment point varied from 45 to 90 (± 5) days post-injury over the 10-year study. These data points were mutually exclusive, so they were combined as day 45/90 in the analysis. There were cases with missing data at one or more time points. Across all time points for all participants, 85% of data were complete. To account for the missing data, multiple imputation with 20 imputations was used (Rubin, 1987). This method is widely accepted in the biostatistics community and has been effectively used in studies previously published by our research group (McCrea et al., 2003).

Symptom, cognitive, and postural stability recovery curves for the three groups were created with 95% confidence intervals based on the estimated model. Since multiple testing was performed at each time point, Dunn-Sidak correction was considered to control Type I error. Using this conservative correction, we used a 0.002 level of significance for the *post hoc* comparisons on data from the GSC, SAC and BESS and 0.004 for the neurocognitive tests.

In addition, univariate logistic regression was used to identify risk factors associated with prolonged recovery (i.e., prolonged recovery group vs. typical recovery group). Multivariate logistic regression was not considered because some of the potential risk factors are highly correlated. Factors included in the regression model are listed in Table 4. A second logistic regression was implemented to investigate potential risk factors associated with prolonged recovery at day 45/90. For all logistic regression analyses, no imputation for missing values was used. All analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Incidence of Typical vs. Prolonged Recovery

Applying the study's empirically derived criteria, 90% ($n = 513$) of injured athletes were classified as the typical recovery group and 10% ($n = 57$) as the prolonged recovery group.

Table 1 provides a comparison of characteristics for the three study groups. As expected based on our matching algorithms, there were no statistically significant differences between the two injured groups or the control group on demographic (except for height), concussion history, or baseline test performance variables used to match control and injured subjects. The two injured and control groups were also not statistically different at baseline from the larger group of athletes enrolled in the study.

Typical vs. Prolonged Recovery Course

The prolonged recovery group had a significantly longer time course of recovery in symptoms, cognitive functioning and postural stability that was clearly distinct from the typical recovery group and control group.

As expected from the classification criteria, the prolonged recovery group had a longer course of symptoms than the typical recovery group. The prolonged recovery group reported more severe symptoms than the control group and typical recovery group at all assessment points from time of injury through day 45/90 post-injury (group \times time interaction; $p < .001$) (see Figure 1). The typical recovery group reported higher symptom levels than the control group through day 3 post-injury ($p < .0001$), without significantly elevated symptoms at day 5 or thereafter.

Beyond self-reported symptoms, the prolonged recovery group also showed a pattern of more severe and persistent cognitive impairment on standardized testing than the typical

Table 1. Comparison of sample characteristics for typical recovery group, prolonged recovery group, and control group

Characteristic	Mean (95% CI)			<i>p</i>
	Typical recovery group ($n = 513$)	Prolonged recovery group ($n = 57$)	Control group ($n = 166$)	
Demographics				
Age (y)	17.51 (17.32–17.69)	17.04 (16.41–17.66)	17.39 (17.11–17.68)	.25
Academic year (1–4)	2.53 (2.35–2.72)	2.75 (1.93–3.57)	2.66 (2.33–2.99)	.54
Height (in)	70.65 (70.25–71.04)	70.09 (68.97–71.22)	71.52 (70.98–72.06)	.04
Body weight (lbs)	191.00 (186.81–195.19)	186.29 (173.39–199.19)	196.50 (189.44–203.56)	.30
Years played sport (y)	8.97 (8.54–9.40)	8.58 (5.85–11.31)	8.42 (7.67–9.16)	.44
Self-reported concussion history				
Prior concussions – total (average per subject)	0.51 (0.41–0.61)	0.41 (0.15–0.66)	0.33 (0.20–0.46)	.49
Prior concussions – sport-related (average per subject)	0.40 (0.32–0.49)	0.22 (0.04–0.40)	0.30 (0.19–0.41)	.15
Baseline test results				
GSC total score	4.23 (3.58–4.89)	3.24 (1.69–4.79)	3.94 (2.79–5.09)	.60
SAC total score	27.00 (26.78–27.22)	27.05 (26.39–27.72)	26.92 (26.63–27.22)	.89
BESS total score	10.98 (10.26–11.70)	12.06 (10.54–13.57)	13.89 (13.09–14.69)	.30
HVLT Immediate	25.15 (24.34–25.95)	22.70 (20.15–25.25)	25.31 (24.23–26.40)	.18
HVLT Delayed Recall	8.72 (8.31–9.12)	8.20 (6.95–9.45)	9.15 (8.58–9.72)	.29
HVLT Recognition	22.71 (22.36–23.06)	22.42 (21.43–23.37)	22.94 (22.60–23.28)	.55
Trail Making Test- B	65.41 (61.41–69.41)	68.82 (51.77–85.88)	57.30 (52.30–62.31)	.05
SDMT	55.62 (53.42–57.82)	52.31 (42.87–61.73)	58.90 (55.63–62.16)	.13
Stroop Color Word	46.95 (45.28–48.63)	48.71 (43.89–53.51)	48.66 (46.05–51.27)	.48

Note. For academic year, value indicates year in high school or college for total combined sample.

GSC = Graded Symptom Checklist; SAC = Standardized Assessment of Concussion; BESS = Balance Error Scoring System; HVLT = Hopkins Verbal Learning Test; SDMT = Symbol Digit Modalities Test; 95% CI = 95% confidence interval.

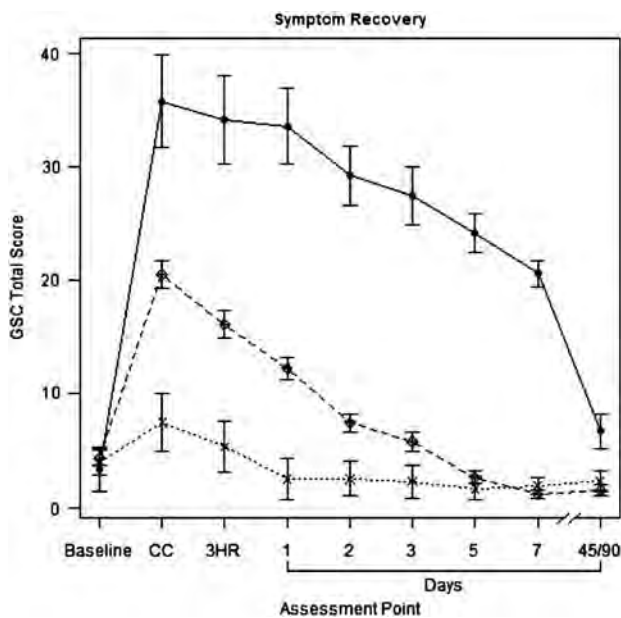


Fig. 1. Symptom recovery curve comparing typical recovery (open circles), prolonged recovery (filled circles), and normal control (Xs) groups. Group \times time interaction, $p < .001$. Higher scores indicate more severe symptoms on the GSC. GSC = Graded Symptom Checklist; CC = time of concussion; 3 HR = 3 hours post-injury. Error bars indicate 95% confidence interval.

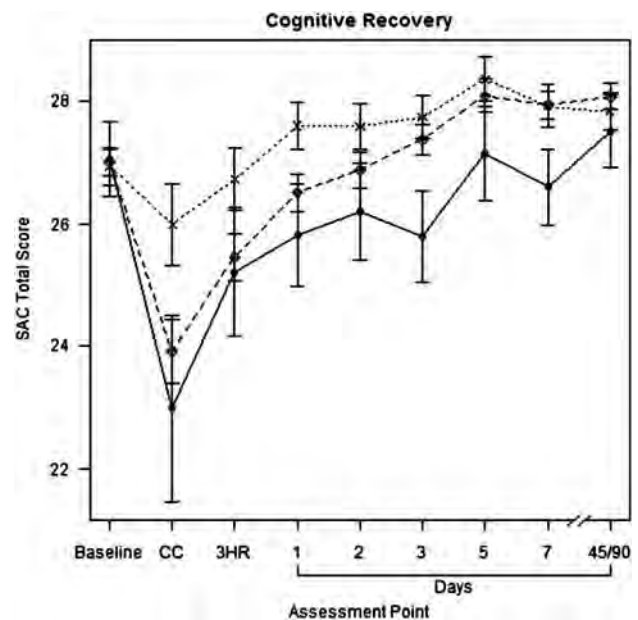


Fig. 2. Cognitive recovery curve comparing typical recovery (open circles), prolonged recovery (filled circles), and normal control (Xs) groups. Group \times time interaction, $p < .001$. Lower scores indicate poorer cognitive test performance on the SAC. SAC = Standardized Assessment of Concussion; CC = time of concussion; 3 HR = 3 hours post-injury. Error bars indicate 95% confidence interval.

recovery group and control group, as measured by performance on the SAC (group \times time interaction, $p < .001$) (see Figure 2). The prolonged recovery group performed poorer than the typical recovery group and control group on the SAC through day 7 post-injury ($p < .0001$), while the typical recovery group showed cognitive recovery on the SAC relative to controls by day 2 post-injury. There were no significant group differences on the SAC at day 45/90.

Among the neurocognitive measures, only a few significant group findings were identified and there were no significant interactions (group \times day effects; all p -values $> .08$). Applying our conservative correction for level of statistical significance ($p < .004$), the prolonged recovery group showed significantly lower immediate memory scores on the Hopkins Verbal Learning Test (HVLIT Immediate Memory) than the typical group (estimated difference: -2.88 ; 95% CI: -1.00 to -4.76 ; $p = .0028$) at day 6–7, but neither the typical or atypical recovery groups showed a statistically significant difference from the control group. For the other neuropsychological measures, we did not find any statistically significant group differences at any time points (see Table 3).

The prolonged and typical recovery groups performed more poorly than controls on postural stability testing immediately after injury ($p < .001$) (see Figure 3 and Table 2), but there were no differences between the prolonged and recovery group. There were no statistically significant group differences on balance testing beyond 3 hr post-injury.

Tables 2 and 3 provides detailed data on estimated differences and effect sizes between the typical recovery, prolonged recovery and control groups on the GSC, SAC, BESS,

and neuropsychological tests at each post-injury assessment point. Overall, the prolonged recovery group reported elevated symptoms that persisted through the day 45/90 time

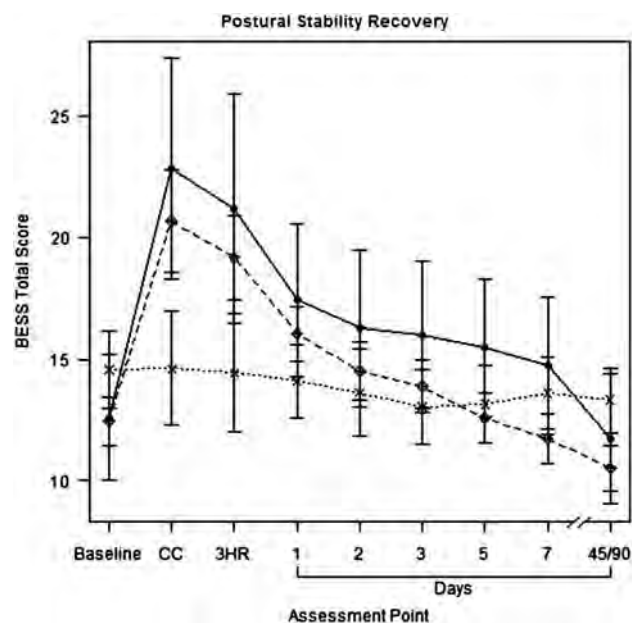


Fig. 3. Postural stability recovery curve comparing typical recovery (open circles), prolonged recovery (filled circles), and normal control (Xs) groups. Group \times time interaction, $p < .001$. Higher scores indicate poorer balance test performance on the BESS. BESS = Balance Error Scoring System; CC = time of concussion; 3 HR = 3 hours post-injury. Error bars indicate 95% confidence interval.

Table 2. Estimated differences among typical recovery group, prolonged recovery group, and control group on GSC, SAC, and BESS

Time	Comparison	Symptoms (GSC score)				Cognitive function (SAC score)				Postural stability (BESS score)			
		Estimate	95% CI	Effect size	<i>P</i> value	Estimate	95% CI	Effect size	<i>p</i> value	Estimate	95% CI	Effect size	<i>p</i> value
BL	Typical vs. Control	0.38	(-0.95, 1.71)	0.05	.5747	0.06	(-0.31, 0.43)	0.03	.7376	-2.12	(-4.01, -0.23)	-0.29	.031
	Prolonged vs. Typical	-1.04	(-3.1, 1.02)	-0.15	.1607	0.05	(-0.6, 0.7)	0.03	.8741	0.15	(-2.66, 2.96)	0.03	.9155
	Prolonged vs. Control	-0.66	(-2.91, 1.59)	-0.10	.5699	0.12	(-0.57, 0.81)	0.06	.7384	-1.97	(-4.81, 0.88)	-0.30	.1763
CC	Typical vs. Control	13.03	(10.25, 15.81)	1.08	<.0001	-2.07	(-2.93, -1.21)	-0.57	<.0001	6.07	(2.95, 9.19)	0.53	.0002
	Prolonged vs. Typical	15.27	(11.06, 19.48)	0.95	<.0001	-0.93	(-2.52, 0.66)	-0.22	.2531	2.17	(-2.85, 7.19)	0.18	.3979
	Prolonged vs. Control	28.29	(23.45, 33.13)	1.93	<.0001	-3.01	(-4.72, -1.3)	-0.79	.0007	8.24	(3.16, 13.32)	0.79	.0017
3HR	Typical vs. Control	10.75	(8.22, 13.28)	0.95	<.0001	-1.27	(-1.88, -0.66)	-0.47	<.0001	4.74	(1.77, 7.7)	0.42	.0023
	Prolonged vs. Typical	18.05	(13.99, 22.11)	1.11	<.0001	-0.24	(-1.38, 0.9)	-0.08	.6775	2.00	(-2.86, 6.87)	0.18	.4208
	Prolonged vs. Control	28.80	(24.21, 33.39)	2.01	<.0001	-1.51	(-2.67, -0.35)	-0.55	.0115	6.74	(1.48, 12)	0.64	.0135
D1	Typical vs. Control	9.72	(7.62, 11.82)	1.03	<.0001	-1.09	(-1.58, -0.6)	-0.48	<.0001	1.95	(0.08, 3.82)	0.21	.0418
	Prolonged vs. Typical	21.35	(17.88, 24.82)	1.45	<.0001	-0.68	(-1.56, 0.2)	-0.23	.1333	1.38	(-1.92, 4.68)	0.16	.4129
	Prolonged vs. Control	31.07	(27.19, 34.95)	2.46	<.0001	-1.77	(-2.69, -0.85)	-0.66	.0002	3.33	(-0.17, 6.84)	0.39	.063
D2	Typical vs. Control	4.94	(3.2, 6.68)	0.64	<.0001	-0.72	(-1.17, -0.27)	-0.35	.0024	0.90	(-1.31, 3.1)	0.09	.4258
	Prolonged vs. Typical	21.81	(19.07, 24.55)	1.64	<.0001	-0.68	(-1.5, 0.14)	-0.27	.1095	1.74	(-1.6, 5.08)	0.22	.3069
	Prolonged vs. Control	26.74	(23.72, 29.76)	2.20	<.0001	-1.39	(-2.25, -0.53)	-0.59	.0018	2.64	(-1.07, 6.36)	0.31	.1646
D3	Typical vs. Control	3.51	(1.82, 5.2)	0.47	<.0001	-0.37	(-0.8, 0.06)	-0.19	.095	0.85	(-1.03, 2.73)	0.10	.3777
	Prolonged vs. Typical	21.70	(19.03, 24.37)	1.68	<.0001	-1.58	(-2.36, -0.8)	-0.57	<.0001	2.13	(-1.07, 5.33)	0.26	.1933
	Prolonged vs. Control	25.21	(22.29, 28.13)	2.13	<.0001	-1.96	(-2.78, -1.14)	-0.72	<.0001	2.98	(-0.46, 6.41)	0.39	.0904
D5	Typical vs. Control	0.97	(-0.19, 2.13)	0.21	.1027	-0.27	(-0.72, 0.18)	-0.13	.2284	-0.57	(-2.49, 1.34)	-0.07	.5582
	Prolonged vs. Typical	21.51	(19.75, 23.27)	1.94	<.0001	-0.94	(-1.74, -0.14)	-0.35	.0224	2.91	(-0.1, 5.92)	0.38	.0591
	Prolonged vs. Control	22.48	(20.52, 24.44)	2.05	<.0001	-1.21	(-2.05, -0.37)	-0.49	.0049	2.33	(-0.92, 5.59)	0.30	.1611
D7	Typical vs. Control	-0.79	(-1.63, 0.05)	-0.24	.0714	0.01	(-0.4, 0.42)	0.01	.9499	-1.89	(-3.67, -0.1)	-0.22	.0385
	Prolonged vs. Typical	19.45	(18.2, 20.7)	2.07	<.0001	-1.34	(-2.01, -0.67)	-0.62	<.0001	3.00	(0, 5.99)	0.37	.0505
	Prolonged vs. Control	18.67	(17.26, 20.08)	1.94	<.0001	-1.33	(-2.04, -0.62)	-0.59	.0003	1.11	(-2.07, 4.3)	0.13	.4945
D45/90	Typical vs. Control	-0.86	(-1.88, 0.16)	-0.16	.098	0.24	(-0.13, 0.61)	0.14	.1986	-2.81	(-4.47, -1.15)	-0.34	.001
	Prolonged vs. Typical	5.21	(3.62, 6.8)	0.65	<.0001	-0.57	(-1.2, 0.06)	-0.31	.0799	1.20	(-1.64, 4.04)	0.18	.4063
	Prolonged vs. Control	4.35	(2.59, 6.11)	0.50	<.0001	-0.32	(-1.01, 0.37)	-0.16	.3506	-1.61	(-4.61, 1.4)	-0.21	.2953

Note. Bold *p* values < .002.

GSC = Graded Symptom Checklist; SAC = Standardized Assessment of Concussion; BESS = Balance Error Scoring System; BL = Baseline (pre-injury); CC = time of concussion; 3 HR = 3 hours post-injury; D1 = Day 1 post-injury; D2 = Day 2 post-injury; D3 = Day 3 post-injury; Day 5 = Day 5 post-injury; D7 = Day 7 post-injury; D45/90 = Day 45/90 post-injury; 95% CI = 95% confidence interval of estimate.

Table 3. Estimated differences among typical recovery group, prolonged recovery group, and control group on neuropsychological tests

Assessment point	Comparison	HVLTL Immediate Memory				HVLTL Delayed Recall				HVLTL Recognition			
		Estimate	95% CI	Effect size	p value	Estimate	95% CI	Effect size	p value	Estimate	95% CI	Effect size	p value
BL	Typical vs. Control	0.11	(-1.07, 1.29)	0.03	.8594	-0.04	(-0.59, 0.52)	-0.02	.9023	0.02	(-0.39, 0.44)	0.01	.9167
	Prolonged vs. Typical	-1.72	(-3.98, 0.54)	-0.41	.1382	-0.46	(-1.58, 0.66)	-0.21	.4233	-0.28	(-1.09, 0.53)	-0.18	.5006
	Prolonged vs. Control	-1.61	(-3.93, 0.71)	-0.4	.1754	-0.49	(-1.58, 0.59)	-0.23	.3719	-0.26	(-1.04, 0.52)	-0.18	.5192
D1-2	Typical vs. Control	-1.1	(-2.18, -0.03)	-0.25	.0449	-0.49	(-1.06, 0.09)	-0.2	.0968	-0.52	(-0.96, -0.07)	-0.28	.0238
	Prolonged vs. Typical	-1.29	(-3.26, 0.68)	-0.29	.1997	-0.78	(-1.84, 0.28)	-0.32	.1497	0	(-0.81, 0.82)	0	.9968
	Prolonged vs. Control	-2.39	(-4.44, -0.35)	-0.57	.0222	-1.27	(-2.36, -0.18)	-0.55	.0233	-0.51	(-1.36, 0.33)	-0.32	.2327
D6-7	Typical vs. Control	0.45	(-0.58, 1.47)	0.1	.3927	0.16	(-0.49, 0.82)	0.06	.6271	0.35	(-0.11, 0.82)	0.19	.1375
	Prolonged vs. Typical	-2.88	(-4.76, -1.00)	-0.65	.0028	-1.35	(-2.53, -0.16)	-0.46	.0261	-0.79	(-1.61, 0.03)	-0.44	.06
	Prolonged vs. Control	-2.43	(-4.37, -0.5)	-0.54	.0141	-1.19	(-2.41, 0.04)	-0.39	.0591	-0.43	(-1.3, 0.43)	-0.21	.3236
D45/90	Typical vs. Control	-0.21	(-1.16, 0.73)	-0.05	.6578	0.1	(-0.46, 0.67)	0.04	.7208	0.16	(-0.27, 0.59)	0.09	.4699
	Prolonged vs. Typical	-2.03	(-3.89, -0.18)	-0.45	.0321	-0.58	(-1.66, 0.49)	-0.25	.2857	-0.62	(-1.44, 0.19)	-0.33	.1337
	Prolonged vs. Control	-2.25	(-4.16, -0.34)	-0.49	.0213	-0.48	(-1.58, 0.61)	-0.21	.3896	-0.47	(-1.29, 0.36)	-0.29	.2709
Assessment point	Comparison	Symbol Digit Modalities Test				Trail Marking Test – Part B				Stroop Color-Word Test			
		Estimate	95% CI	Effect size	p Value	Estimate	95% CI	Effect size	p value	Estimate	95% CI	Effect size	p value
BL	Typical vs. Control	-1.22	(-4.35, 1.91)	-0.1	.4463	5.15	(-0.76, 11.06)	0.25	.091	-0.43	(-2.85, 2)	-0.05	.7306
	Prolonged vs. Typical	-2.3	(-8.31, 3.71)	-0.19	.4543	3.99	(-8.09, 16.07)	0.18	.5194	0.46	(-4.1, 5.03)	0.05	.8423
	Prolonged vs. Control	-3.52	(-9.49, 2.45)	-0.29	.2492	9.14	(-2.65, 20.93)	0.43	.1318	0.04	(-4.53, 4.61)	0	.9874
D1-2	Typical vs. Control	-2.85	(-5.65, -0.05)	-0.25	.0474	4.98	(0, 9.95)	0.25	.0514	-1.3	(-3.63, 1.03)	-0.14	.2766
	Prolonged vs. Typical	-2.96	(-7.96, 2.05)	-0.27	.2474	-3.04	(-11.66, 5.59)	-0.17	.4902	1.77	(-2.6, 6.13)	0.17	.4284
	Prolonged vs. Control	-5.81	(-10.92, -0.69)	-0.54	.0265	1.94	(-7.08, 10.96)	0.12	.674	0.47	(-4.02, 4.96)	0.05	.8374
D6-7	Typical vs. Control	-0.26	(-3.05, 2.52)	-0.02	.8526	5.35	(1.32, 9.38)	0.32	.0097	0.13	(-2.31, 2.58)	0.01	.9142
	Prolonged vs. Typical	-3.71	(-8.43, 1.01)	-0.36	.1236	2.29	(-5.14, 9.72)	0.13	.5465	0.37	(-4.19, 4.92)	0.04	.8746
	Prolonged vs. Control	-3.97	(-8.96, 1.01)	-0.36	.1185	7.64	(-0.04, 15.31)	0.44	.0515	0.5	(-4.2, 5.21)	0.05	.8344
D45/90	Typical vs. Control	0.49	(-2.15, 3.13)	0.04	.7138	3.91	(-0.15, 7.97)	0.24	.0597	-0.42	(-2.8, 1.95)	-0.04	.7289
	Prolonged vs. Typical	-5.97	(-11.14, -0.8)	-0.58	.024	4.65	(-3.02, 12.31)	0.24	.2351	0.73	(-3.91, 5.36)	0.06	.7591
	Prolonged vs. Control	-5.47	(-10.75, -0.19)	-0.52	.0426	8.56	(0.76, 16.36)	0.45	.0319	0.31	(-4.43, 5.04)	0.02	.8995

Note. Bold p values < .004.

HVLT = Hopkins Verbal Learning Test; BL = Baseline (pre-injury); CC = time of concussion; 3 HR = 3 hours post-injury; D1 = Day 1 post-injury; D2 = Day 2 post-injury; D3 = Day 3 post-injury; Day 5 = Day 5 post-injury; D7 = Day 7 post-injury; D45/90 = Day 45/90 post-injury. 95% CI = 95% confidence interval of estimate.

Table 4. Results of univariate logistic regression on factors associated with prolonged recovery

Category	Categorical variables	Odds ratio (95% CI)		p
Demographics	Gender (male)	1.736	(0.83, 3.63)	.1422
Participation	Sport			
	Soccer (reference)	1.000		
	Football	0.872	(0.36, 2.11)	.1342
	Hockey	2.960	(0.27, 31.91)	.4543
	Lacrosse	2.130	(0.67, 6.74)	.4737
	Level of competition			
	College (reference)	1.000		
	High school	1.318	(0.73, 2.37)	.3565
	Sport orientation			
	Offense (reference)	1.000		
	Defense	1.217	(0.47, 3.13)	.6825
Mechanism of injury	Being tackled by opponent	0.584	(0.23, 1.51)	.2684
	Tackling opponent	1.696	(0.92, 3.12)	.0897
	Collision with opponent	0.752	(0.42, 1.35)	.3376
	Contact with ground	2.008	(0.92, 4.38)	.0792
	Contact with barrier (e.g., goal)	0.509	(0.07, 3.9)	.5158
	Contact with ball	2.143	(0.67, 6.82)	.1966
	Blocking	0.556	(0.19, 1.59)	.2748
Acute injury characteristics	Loss of consciousness	4.152	(2.12, 8.15)	<.0001
	Posttraumatic amnesia	1.814	(1.00, 3.28)	.0489
	Retrograde amnesia	2.190	(1.18, 4.06)	.0128
Concussion history	Same season repeat concussion	1.141	(0.57, 2.31)	.7133
Category	Continuous variables	Estimate (95% CI)		p
Demographics	Age	−0.134	(−0.28, 0.01)	.0651
	Height	−0.018	(−0.07, 0.03)	.5035
	Weight	−0.001	(−0.01, 0.01)	.6453
GSC scores	Baseline	−0.022	(−0.07, 0.02)	.3311
	Time of concussion	0.047	(0.03, 0.06)	<.0001
	2–3 hours post	0.053	(0.04, 0.07)	<.0001
	Day 1 post	0.071	(0.05, 0.09)	<.0001
SAC scores	Baseline	0.001	(−0.17, 0.17)	.9904
	Time of concussion	−0.042	(−0.12, 0.03)	.2819
	2–3 hours post	−0.055	(−0.18, 0.07)	.3853
	Day 1 post	−0.086	(−0.20, 0.03)	.1507
BESS scores	Baseline	0.004	(−0.05, 0.06)	.8939
	Time of concussion	0.012	(−0.02, 0.05)	.5256
	2–3 hours post	0.016	(−0.02, 0.05)	.4087
	Day 1 post	0.017	(−0.02, 0.05)	.3726
Injury management	Total time symptom free before return	0.005	(0.001, 0.009)	.0007
	Total time withheld from competition	0.024	(0.008, 0.040)	.0016
Concussion history	Total number of prior concussions	−0.167	(−0.59, 0.26)	.4435

Note. Bold *p* values < .05.

GSC = Graded Symptom Checklist; SAC = Standardized Assessment of Concussion; BESS = Balance Error Scoring System; 95% CI = 95 percent confidence interval of odds ratio or estimate.

point, but there were no statistically significant residual impairments on performance based measures of cognitive functioning or balance 45/90 days post-injury.

Factors Associated With Prolonged Recovery

Acute injury characteristics of unconsciousness ($p < .0001$), posttraumatic amnesia ($p = .049$), retrograde amnesia ($p = .013$) and symptom severity within the first 24 hr of injury ($p < .0001$)

were the factors most strongly associated with prolonged recovery (see Table 4). When present, the period of unconsciousness had a maximum of a few seconds and the period of amnesia had a maximum of several minutes. Demographic variables, level of competition, player position, mechanism of injury, concussion history, and acute scores on the SAC and BESS were not predictive of prolonged recovery time.

Athletes who were rendered unconscious had 4.15 times (95% CI, 2.12 to 8.15) higher odds of prolonged recovery

than those with no loss of consciousness. Retrograde amnesia was associated with 2.19 times (95% CI, 1.18 to 4.06) higher odds and posttraumatic amnesia 1.81 times (95% CI, 1.00 to 3.28) higher odds for prolonged recovery.

Based on symptom severity at the most acute time point immediately following concussion, individuals with an increase of 20 points or more over baseline on the GSC had 2.56 times (95% CI, 1.80 to 3.64; $p < .0001$) greater risk of prolonged recovery at day 7. Individuals with an increase of 20 points or higher on the GSC at the 2–3 hr assessment point and on day 1, respectively, had 2.89 (95% CI, 2.03 to 4.11; $p < .0001$) and 4.14 (95% CI, 2.80 to 6.11; $p < .0001$) times higher risk of prolonged recovery at day 7.

The total length of time a player was withheld from competition ($p = .0016$) and the duration of a symptom free waiting period ($p = .0007$) after concussion were inversely associated with a reduced risk of prolonged recovery. That is, the longer a player was withheld from competition and allowed a symptom free waiting period, the lower their risks of prolonged recovery.

At 45/90 days post-injury, 23% ($n = 13$) of the prolonged recovery group continued to report symptom scores higher than the normative-based criterion for recovery (outside the 95th percentile of the control group change score from baseline to day 45/90). This figure compares to just 5% of the typical recovery group ($n = 26$), which is equivalent to the “false positive” rate in the control group. The difference in frequency of persistent symptoms between the typical recovery group and prolonged recovery group at day 45/90 was statistically significant ($\chi^2 = 21.08$; $p < .001$).

None of the specific variables reached statistical significance in the second logistic regression on factors associated with continued definition of prolonged recovery at day 45/90.

DISCUSSION

This study reports major findings from the largest prospectively collected dataset to appear in the literature on the incidence, course, and predictors of prolonged recovery time following sport related concussion. In our study sample, 10% of injured athletes exhibited postconcussive symptoms that persisted beyond the typical seven day window of recovery commonly reported in group studies. The prolonged recovery group demonstrated a different pattern and course of recovery than the typical recovery group, evidenced by symptoms and cognitive dysfunction that were more pronounced during the acute period and persisted over a lengthier period of time than that observed in the typical recovery group. Nearly a quarter of those athletes who failed to meet the criteria of recovery within 1 week (2.3% of the total injured sample) continued to report elevated symptoms 6 to 12 weeks post-injury.

Despite the report of persistent symptoms 45–90 days post-injury in the prolonged recovery group, there were no statistically significant deficits that persisted on objective neuropsychological or postural stability testing, suggesting that functional impairment 2–3 months following concussion

is likely minimal. The differences between the two groups on measures of balance acutely were relatively small, with no group differences evident by day 6–7, and the two groups differed on only 2 of 7 cognitive measures at day 6–7, with no evidence of residual impairments on performance based measures of cognitive functioning and balance 45–90 days after concussion.

Results from the current study have potential public health implications when applied in the context of concussion as a common injury in many organized sports and recreational activities. Our methodology involved the use of a 95% one-way confidence interval using self-reported symptoms in a control sample to define prolonged recovery, so it is important to recognize that we have a defined 5% false positive rate in our prolonged recovery group. If we conservatively apply our current findings of a 5% “true” prolonged recovery incidence to previous epidemiologic estimates of 300,000 concussions occurring annually in organized sports in the United States (Thurman, Branche, & Sniezek, 1998), that would suggest that 15,000 young athletes continue to experience symptoms and functional impairments beyond 1 week after concussion, and that 3750 athletes continue to experience persistent symptoms for at least several weeks after concussion. If we apply our findings to larger estimates of 3.8 million concussions due to sport and recreational activities each year (Langlois et al., 2006), those figures expand to 190,000 individuals experiencing symptoms and other postconcussive problems beyond 1 week and nearly 50,000 individuals still affected by symptoms several weeks after their injury.

In addition to our findings on the frequency and time course of prolonged recovery, this study identified certain predictive factors associated with persistent symptoms. Our findings suggest acute injury severity, marked by unconsciousness, amnesia and elevated initial symptom severity significantly increases an athlete’s risk of prolonged recovery time. The presence of acute injury characteristics of unconsciousness and amnesia significantly increased the risk of an athlete requiring longer than the typical seven day window to achieve a full recovery. Thus, more severe injuries were associated with more severe and longer lasting symptoms, as well as deficits in cognitive functioning and postural stability. Our findings are consistent with a recent study reporting that persistent symptom increases in children one year after mTBI were more common among children who had a period of unconsciousness and abnormalities on neuroimaging associated with their mTBI (Yeates et al., 2012).

Of interest, an athlete’s risk of prolonged recovery following concussion was not predicted on the basis of variables relevant to their level or type of participation (e.g., high school vs. college), the mechanism of their concussion, or their prior concussion history. With regard to the influence of specific injury management strategies, the directionality of our findings (i.e., lengthier time withheld from competition in the prolonged recovery group) suggests that prolonged recovery predicted how long a clinician withheld the athlete from returning to competition, rather than vice versa.

This dampens speculation of a reverse finding that prematurely returning to participation accounted for worsening or extended symptoms in our study sample. Beyond the large set of variables included in our regression analysis, we are unable to determine the association between certain non-injury (e.g., psychological factors, other etiologies) and prolonged symptom reporting in our sample, which represents an important question for future studies to address.

These findings move forward the existing evidence base for clinical management of sport related concussion. One of the greatest challenges faced by sports medicine clinicians is determining an athlete's expected course of recovery, which has implications for clinical management and return to play decision making. Our findings suggest that acute injury characteristics, symptom severity, and performance on functional assessments during the acute period are predictive of an athlete's eventual recovery time. In addition to recognizing the importance of acute injury characteristics of unconsciousness and amnesia, our findings also support the call for greater emphasis on methods for assessing the severity of symptoms, cognitive dysfunction, postural instability, and other functional impairments during the acute phase that will assist the clinician in monitoring an athlete's level of recovery and fitness to safely return to competition. Ideally, future research will produce algorithms that effectively predict for clinicians an athlete's likely risk of prolonged recovery and guide clinical decision making to improve safety in return to play.

For the current study, we specifically elected to stratify athletes into the typical recovery group or the prolonged recovery group based on their symptom recovery time because we were directly interested in the indicator relied on most commonly in the setting of clinicians monitoring an athlete's level of recovery and fitness to return to play. This stratification then allowed us to compare recovery on *performance based* measures of cognitive function and balance in athletes with typical and prolonged symptom recovery. While it is commonly thought that athletes are inclined to under-report their symptoms in hopes of more quickly being cleared to return to competition, results from the current study indicate significant overlap in the time course of self-reported and performance based metrics of recovery in the overwhelming majority of athletes. Furthermore, our results also indicate a higher likelihood of persistent subjective symptoms further out from injury (e.g., 45–90 days post-injury), in the absence of impairments on cognitive or balance testing, which is counter to the common stereotype.

Several limitations of the current study require consideration. First, our findings speak only to the lingering effects from a single, uncomplicated concussion during a period of several weeks. The larger public health concern is whether exposure to recurrent concussion may predispose athletes to risks of chronic symptoms, cumulative cognitive impairment or premature onset of degenerative dementia syndromes. We concur with the call for large prospective studies on the true incidence, risk factors, mechanism and underlying pathophysiology of possible late-life effects of recurrent trauma, whether this is due to recurrent concussion or to

exposure to recurrent sub-concussive head trauma. It should also be acknowledged that nearly 90% of the sample included in this study was male and approximately 80% of the injuries studied were in American football. There is a clear need for larger scale studies looking at the effects of gender on recovery, as well as the complexion of concussion across a broader array of sports other than American football. It should also be recognized that the figure of 10% of athletes with prolonged recovery includes a known 5% “false positive” rate, as prolonged recovery was defined as symptom elevation greater than 95% of uninjured control levels. We elected this methodology based on what we considered to be empirically appropriate to define “typical recovery” based on GSC score, while also allowing for the modest psychometric variability of the scale even among normal, non-concussed athletes. Further study is required to determine if educational and policy making initiatives to raise awareness about sport-related concussion over the last 10 years would influence the results of our study now (e.g., result in a higher rate of prolonged recovery due to influences on symptom reporting *vs.* result in lower rate of prolonged recovery due to improved injury management strategies).

Additionally, studies of this type are often not, from an ethical and human safety standpoint, able to be carried out as truly randomized, controlled trials (RCTs). Because an athlete's assignment to the typical or prolonged recovery group was based on our empirically-derived criteria and did not involve any stratified intervention, random group assignment was not readily applicable in this study. We were prohibited by the authorizing human protection boards from prescribing injury management strategies that dictated how long an athlete was withheld from competition after injury, though prolonged recovery did not appear to be associated with athletes being prematurely returned to competition after concussion. Although the control group in this study was not randomly selected in the true sense, our approach to control sampling resulted in very tight matching of the three study groups. We achieved a matched control group sample that provided us adequate power for statistical analysis, so amassing 570 controls was not necessary.

Despite these limitations, several factors contribute to the utility of this study in expanding the existing knowledge base on the true natural history of concussion. First, previous studies have been significantly limited in their scope, sample size, or methodology. Many studies have not included pre-injury baseline assessments, a control group, standardized outcome measures beyond self-reported symptoms, or longitudinal follow-up of injured athletes. Our protocol involved extensive, multi-dimensional assessments at pre-injury baseline and numerous post-injury time points to establish a continuous time course of recovery. Including a large control group allowed us to examine the frequency and variability of postconcussive symptoms among non-injured athletes and factor in the incidence of “false positives” in the current study. Furthermore, we collected an exhaustive information base on hundreds of variables relevant to the acute injury, athlete, environment, and outcome that allowed us to prospectively

investigate the factors associated with recovery, which prior studies have not been able to do on a comprehensive scale.

CONCLUSION

In conclusion, findings from this study of a large sample of high school and collegiate athletes affected by sport related concussion suggest that a subset of athletes experience symptoms and other functional impairments that persist beyond the typical 7-day window of recovery and may extend out at least several weeks in a small percentage of athletes. Although prolonged recovery was associated with the report of elevated symptoms 45 to 90 days post-injury, there was no evidence of residual impairments on performance-based measures of cognitive functioning and balance. Prolonged symptom reporting was associated with markers of acute injury severity. Further study is required to clarify the lengthier course of persistent symptoms in this subset of athletes beyond the three month point, and to identifying other factors that may contribute to prolonged symptom reporting. This may help guide interventional strategies for those athletes who fail to make the typical rapid recovery from sport-related concussion.

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BAILES

EXHIBIT 11



What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes?

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ABSTRACT

Objective The purpose of this paper was to review the current state of evidence for chronic traumatic encephalopathy (CTE) in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

Data sources MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury.

Results At present, there are no published epidemiological, cross-sectional or prospective studies relating to modern CTE. Owing to the nature of the published studies, being case reports or pathological case series, it is not possible to determine the causality or risk factors with any certainty. As such, the speculation that repeated concussion or subconcussive impacts cause CTE remains unproven. The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature.

Conclusions At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic.

INTRODUCTION

Considerable attention surrounds the potential for long-term problems in athletes with high exposure to head impacts during a career in collision sport.¹ There is evidence^{2–4} supporting an association between long-term cognitive, neurobehavioural, psychiatric problems and participation in sport.⁵ Given that sports-related concussion is a common injury and that concussive or subconcussive blows to the head or body are an inevitable consequence of sports participation, if a causal relationship between these impacts and later-life neuropsychiatric disease exists, then potentially an enormous number of retired athletes would be at risk.⁶ Based on the published case studies, however, one estimate is that fewer than 4% of retired US professional football players may be at risk for this condition⁷ rather than all exposed athletes, raising the issue that this may not be a part of impact exposure but rather due to other as yet unidentified factors.

A recent report by McKee *et al*⁸ has suggested that chronic traumatic encephalopathy (CTE) may represent a unique tauopathy with characteristic pathological stages; however, the published methodology does not allow a causal relationship to be determined between concussion or subconcussive impacts being a risk factor for CTE.

The purpose of this paper was to review the current state of evidence for CTE in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

METHODS

Articles were retrieved via online database searching, hand-searching reference lists and cited reference searches. The online databases of MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus were searched. Key words, MeSH terms and combinations of these were used to systematically search the databases. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury (TBI).

CLINICAL SYNDROMES OF LONG-TERM PROBLEMS FOLLOWING CONCUSSION

The clinical characterisation of the presentations of athletes with chronic postconcussive symptoms is poorly defined and may reflect intrinsic differences (eg, genetic) between individuals rather than the oversimplified understanding that these syndromes are due to concussive or subconcussive trauma alone. In some cases, the persistent 'postconcussive' symptoms may, in large part, be due to unrecognised depression or anxiety,⁹ which may be labelled as 'overtraining' or even athlete 'burnout'.¹⁰

If we assume concussion is the acute clinical syndrome with 90–95% of cases recovering in less than 10 days, then there is a small group where *prolonged postconcussive symptoms* exist, that is, where the symptoms persist more than 10 days after a single episode of acute concussion (5–10% of cases) but full recovery eventually ensues usually within a matter of weeks.¹¹ The clinical and neuropsychological features are those of a resolving acute injury and perhaps this entity should be considered as part of the acute syndrome.

In addition to the acute syndrome, a number of distinct but as yet poorly defined clinical subsets exist that may shed light on the process of recovery

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from concussive injury. These subsets are based on clinical experience and are not supported by hard scientific evidence at this time. Nevertheless, it may be useful to consider the full spectrum of presentations of athletes with persistent or permanent symptoms and the terminology of these states.

These include:

- ▶ Prolonged postconcussive symptoms as discussed above.
- ▶ Persistent postconcussion symptoms after one or more concussions where recovery is slow and may take months to years.¹² The DSM-IV criteria for Post Concussion Syndrome is invoked only if the symptoms last beyond 3 months. Approximately 80% of such patients recover fully with time.¹³ Cognitive testing reveals mainly attentional deficits, and structural neuroimaging is normal.
- ▶ Permanent PCS—as per above, but these individuals do not recover fully, and this has been estimated at between 10% and 20% of all cases of persistent concussion symptoms. Functional MR and/or electrophysiological change may be present, but normal structural neuroimaging is typical.¹⁴
- ▶ Proposed CTE where chronic cognitive and/or neurobehavioural dysfunction exists and a pathological diagnosis is subsequently confirmed.^{3 6} It is worth noting that there are cases where the clinical phenotype is the same as pathologically confirmed CTE cases; however, no neuropathological change is demonstrated at autopsy.⁸

As well as these broad categories, there are other athletes who *de novo* manifest mental health issues (depression, anxiety, suicide) or neurobehavioural problems in the absence of persistent or prolonged concussive symptoms dating from the time of an injury. Whether these represent a variant of the subsets above or simply reflect the high incidence of such disorders in society remains to be elucidated. The risk factors for such complications following concussion remain unclear, although they may be related to repeated concussions, at least in retrospective surveys.^{2 15} Prospective studies of head-injured individuals, with neuropathological and clinical verification, are needed to improve understanding of head trauma as a risk factor for sequelae.¹⁶

As well as clinical symptoms, there is some limited objective evidence of persistent neurophysiological, cognitive¹⁶ and radiological¹⁷ deficits up to 30 years following concussion.

PHYSIOLOGY OF CONCUSSION

Understanding the pathophysiology of concussion would be expected to lead to an improvement in the assessment of deficit and recovery following injury, and to facilitate the accurate classification of severity. For example, little is known about the anatomical localisation of common clinical features such as headache, loss of consciousness (LOC), difficulty with concentration, sleep disturbance and fatigue. Moreover, it is currently unknown whether mild TBI reflects a single clinical entity with a linear spectrum of injury or even distinct injury subtypes. It is hoped that this understanding may give some insight into whether *in vivo* diagnosis of CTE is possible.

In animal models following acute injury, the release of neurotransmitters and ionic fluxes occurs (known as the 'neurometabolic cascade'),¹⁸ which in turn leads to changes in cell membrane function. Animal studies suggest that, during the glucose metabolic depression phase (1–10 days postinjury), the brain is more vulnerable to repeat injury.¹⁸ Changes in the intracellular fluid status or the presence of axonal swelling may be detected using imaging techniques such as advanced diffusion weighted imaging (DWI), which also allow mapping of white

matter fibre tracts in the central nervous system.¹⁹ Preliminary studies have demonstrated DWI changes in the acute setting following mild TBI in a small cohort of adolescent patients with normal CT scans as well as in a cohort of asymptomatic professional boxers.²⁰ Functional neuroimaging techniques, for example, functional MRI (fMRI) have demonstrated changes in brain function following sport-related TBI.²¹ The main limitation of this technique is that it only reveals regions of the brain that are active in the specific cognitive task being studied. Another imaging modality, Functional Connectivity, is able to detect realtime resting state networks and may provide an alternative to fMRI for identifying brain subregions and networks that are affected in mild TBI.²² Other techniques such as MR spectroscopy (MRS) allow the detection of metabolic disturbances following mild TBI through the measurement of intracellular metabolites. Preliminary studies in a small cohort of collegiate athletes suggest a role of mitochondrial dysfunction in the postinjury metabolic depression.²³ Other studies using MRS have also demonstrated that the *N*-acetylaspartate/creatine ratio (which reflects neuronal cell damage) is related to injury severity and outcome even when white matter appears normal on MRI.²⁴

DEMENTIA RATES IN THE GENERAL POPULATION

Given that cognitive impairment is one of the key features of the proposed CTE, it is important to understand the risk of this in similar age groups in the general population. The reported incidence and prevalence rates of dementia vary according to the population studied, and prevalence approximately doubles every 5 years from the age of 65 years. The incidence of dementia (all causes) in the 30-year-old to 64-year-old group is 54/100 000, and for the 45-year-old to 64-year-old group, it is 98.1 : 100 000.²⁵

Whether mild, or repetitive mild TBI (mTBI) increases an individual's risk for developing Alzheimer's disease (AD) has been a long-standing topic of contention. While mixed results have been reported regarding the association between moderate and severe TBI and AD, the association between mTBI and AD appears to be less strong. For example, in a systematic review, Bazarian *et al*²⁶ concluded that there was limited support for the notion that mTBI (with LOC) results in an increased risk for later life AD. Further, the authors also concluded that there was insufficient evidence to determine whether an association between mTBI (without LOC) and AD exists.

DEPRESSION IN THE GENERAL POPULATION

Depression and cognitive impairment are both common conditions in older age, and they frequently occur together. A US-based epidemiology study examining major depression reported that the incidence of this disorder in men aged 25–34, 35–44 and 45–54 years was 12.3%, 11.0% and 8.6%, respectively.²⁷ This is much higher among individuals with dementia, where it has been reported that 25–50% of all patients with dementia will develop depression at some point over the course of their illness.^{28 29}

DEPRESSION, COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES IN FORMER ATHLETES

In a study of retired National Football League (NFL) players, responses to questions regarding clinical depression revealed that 269 (11.1%; 95% CI 9.9% to 12.3%) of 2434 respondents reported a previous diagnosis of clinical depression. In comparison to retired NFL players with no history of concussion, retired players with a history of one or two previous

concussions were 1.5 times more likely to be diagnosed with depression, while those with a history of three or more previous concussions were found to be three times more likely to be diagnosed with depression.¹⁵

The results of a screening survey of 513 retired NFL players (average age=61 years) reported that 35% produced scores suggesting a possibly mild cognitive impairment.² In another recent study of former NFL players, the death rate from neurodegenerative diseases was three times greater than that of the general population, although the number of cases in this study was small. More specifically, the rates of diagnosis of AD and amyotrophic lateral sclerosis (ALS) were found to be four times higher in former NFL players than the general population.³⁰ Of the 334 former athletes in this cohort, seven (2.1%) had ALS listed on their death certificates. This issue of ALS is in keeping with the TDP43 tauopathy seen in CTE cases.³¹

BRAIN PATHOLOGY IN NORMAL AGEING

The Honolulu-Asia Aging Study provides a unique longitudinal model of ageing and disease and offers considerable insight into what may be considered *normal ageing* from a pathological standpoint.³² From 1991 to 1993, 3 yearly follow-up clinical and formal neuropsychological examinations have been conducted in 3508 men who were free of dementia and a total of 593 standardised brain autopsies have been conducted.³²

Postmortem brain examination demonstrated diverse pathology, even in individuals clinically diagnosed as 'pure AD,' with fewer than 50% demonstrating the typical pathological features of AD. Furthermore, neuropathological abnormalities were also observed in approximately 40% of neuropsychologically normal patients.³²⁻³⁴ Similarly, disparity between clinical presentation (ie, living diagnosis) and postmortem neuropathology has also been demonstrated in other ageing study samples.³⁵⁻³⁶ It is now clear from these ageing studies that postmortem findings may not represent pathology and may not equate to clinical symptomatology or a syndrome³⁷ and may be seen in cognitively normal older adults. Whether the 'gold standard' of neuropathology in neurological disease is true has been recently questioned.³⁸

THE 'CLASSIC' SYNDROME OF CTE IN PROFESSIONAL BOXERS

In 1928, Dr Harrison Martland first described the 'punch drunk' or CTE state in retired boxers.³⁹ The incidence of classic CTE has proven difficult to establish, due, in the main, to a lack of prospective studies. Roberts,⁴⁰ who randomly sampled 250 retired boxers from a cohort of 16 781 UK boxers registered between 1929 and 1955, reported that in 37 boxers (17%) clinically demonstrable lesions of the nervous system were present. Notably, the oldest boxers in this cohort fought in the late 1800s, in an era where bare-knuckle championships were still conducted, frequent fights occurred even when boxers were concussed and there was little medical supervision or weight matching of boxers; however, only 11 of the 37 cases were elaborated on in this study. A close analysis of the clinical details raises suspicion regarding the certainty of the diagnosis of CTE in most cases.⁴¹

In the published cases, cognitive deterioration was typically detected 10–20 years subsequent to cessation of exposure to repetitive head trauma (ie, postretirement).⁶ Interestingly, in all cases where details were provided, the physical signs but not the cognitive deficits progressed postretirement. There are two distinct clinical syndromes that have been demonstrated in this data set; the first (which occurs in approximately 70% of cases) includes dysarthria, pyramidal problems and cognitive deficits.

As the disease manifests clinically, these cognitive abnormalities include difficulties in memory, information processing speed, insight and orientation. The second clinical syndrome (in approximately 30% of cases) includes dysarthria and pyramidal problems, but with intact cognitive abilities.⁴⁰⁻⁴²⁻⁴⁴ Movement disorders were reported to be present in approximately two in every five reported cases.³

One of the difficulties of ascribing the clinical syndrome solely to boxing is the presence of comorbidities plus risk factors for other conditions that may also result in cognitive deterioration. A case report of a champion boxer with cognitive decline highlights these issues of multifactorial causation of cognitive problems.⁴⁵

The neuropathological features of classic CTE have been described in detail⁴⁶ and typically result in a cavum septum pellucidum with septal fenestration; cerebellar scarring involving Purkinje cell loss and thinning of the granular layer; degeneration of the substantia nigra and locus caeruleus; and diffuse neurofibrillary tangles (NFT) involving the medial temporal region, uncus, amygdala, hippocampus, parahippocampal gyrus and fusiform gyrus along with the more lateral temporal, insular and frontal cortices. The extent of neuropathology appears to be positively correlated with the level of exposure.⁴⁶ Roberts *et al*⁴⁴ examined 14/15 brains originally described by Corsellis *et al*,⁴⁶ as well as six additional boxers' brains using immunocytochemistry, and 19/21 cases also demonstrated widespread diffuse amyloid deposits.

Recently, a propagation model of neurodegeneration has been proposed, suggesting that tau positive NFT phosphorylation may progressively spread from one neuron to adjacent neurons in the absence of ongoing triggering factors.⁴⁷⁻⁵⁰ The implication of this finding is that the neuropathological findings may differ or progress in different stages of the condition. This finding may help resolve the differences between reports of specific sites of tau positive NFT deposition in CTE and other studies that suggest widespread changes.

THE 'MODERN' SYNDROME OF CTE IN FOOTBALLERS

Recent publications³⁻⁵¹ on CTE in retired athletes have introduced a number of conceptual changes in the clinical features⁵²⁻⁵³ and outcomes, and also the neuropathology, as compared with the classic entity described by Roberts⁴⁰ and Corsellis *et al*⁴⁶ in their boxing subjects.

PUBLISHED MODERN CTE CASES

A number of cases of CTE in retired athletes have been published. The index case was reported by Omalu and colleagues in 2005, with additional cases reported subsequently.⁴⁻⁵¹⁻⁵⁴⁻⁵⁶ Recently, the Boston University group published their experience of CTE, with 80 athlete brain donors (22 of whom were also military veterans) with a history of repetitive brain injury, and they found that 80% of these cases demonstrated the characteristic pathology for CTE.⁸

Signs and symptoms

The modern CTE description suggests that symptoms such as gait disorders, speech slowing and extrapyramidal signs may be present; however, neuropsychiatric and behavioural symptoms tend to predominate early.⁵⁷ The most common symptoms reported are mood disorder (mainly depression), paranoia, agitation, social withdrawal, poor judgement and aggression. Cognitive impairment tends to emerge as the major neuropsychiatric feature in the latter stages⁵⁸⁻⁵⁹ and typically includes impairment across the domains of orientation, memory,

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language, attention, information processing speed and executive functioning.⁶⁰ These cognitive symptoms have been proposed to progress in a somewhat predictable manner,³ whereas the classic CTE entity reported little progression of cognitive deficits.⁴⁶

Neuropathology

The reported neuropathological characteristics of both entities (classic and modern CTE) appear to be more closely related and share a number of common features such as fenestrated septum pellucidum, cerebral atrophy, tau+NFT inclusion (although found in greater amounts in modern CTE), β -amyloid deposition (found in less amounts in modern CTE), reduced pigmentation of the substantia nigra and locus caeruleus, and enlarged ventricles. The qualitative description of modern CTE characterises the neuropathological change as also including fronto-temporal lobe atrophy with extensive tau pathology distributed throughout the neocortex, medial temporal lobe, diencephalon, brainstem and spinal cord. In the 51 cases reviewed by Gavett *et al*⁷ 61 diffuse amyloid plaques were found in 24 (47%), neuritic amyloid plaques in 13 (27%) and amyloid angiopathy in 3 (6%). In the Boston study,⁸ amyloid deposition was noted in 44% of the CTE cases.

Although a number of similarities in neuropathological findings have been reported across the modern CTE cases, there are also some important differences. McKee *et al*³ have reported a marked accumulation of tau-immunoreactive astrocytes, but this has not been observed in any of the cases examined by Omalu *et al*.⁶² Omalu *et al*⁶³ have reported the skip-phenomenon, with a propensity to lobar cortical distribution in the absence of prominent periventricular topographic distribution, which has not been described in the McKee *et al*³ cases.

A defining neuropathological feature of the modern CTE entity is abundant filamentous tau lesions, of which the patterns of expression are considered unique, occurring in the absence (or at least relative scarcity) of β -amyloid deposits.³ 8 Prominent filamentous tau inclusions and brain degeneration in the absence of β -amyloid deposits are also considered the sine qua non of a number of neurodegenerative tauopathies. It is worth noting that a number of the degenerative tauopathies, such as behavioural variant fronto-temporal dementia, share many of the clinical and pathological features of 'modern' CTE.^{64–69}

DISCUSSION

The recent autopsy cases differ from the classic CTE description across a number of characteristics including age of onset, progression, assumed predominate (clinical) features and diagnostic criteria. It has also been reported that these recent cases of modern CTE, speculated to be a consequence of concussive and subconcussive blows, are characterised by a distinct neuropathological profile³ 61 63 and manifest primarily as a tauopathy.⁸ Although many of the reported macroscopic neuropathological features are common among the original and newer descriptions of CTE, the different distribution of tau-immunoreactive astrocytes distinguishes the newer description with preferential involvement of the superficial cortical layers occurring on a background of relative scarcity of β -amyloid plaques.

At present, there are no published epidemiological, cross-sectional or prospective studies relating to modern CTE. Owing to the nature of the published studies, being case reports or pathological case series, it is not possible to determine the causality or risk factors with any certainty. As such, the speculation that repeated concussion or subconcussive impacts cause CTE remains unproven.⁷⁰

The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature. In addition, consideration for the potential genetic risk in those athletes with a family history of neurodegenerative disease and the extent to which this contributes to the clinical and pathological profiles also require further investigation.⁴¹

SUMMARY

At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic. Ultimately, scientific research might establish that participation in contact sports leads to a distinct neuropathological syndrome, and this neuropathology causes psychiatric, cognitive and physical problems, but this cause and effect relationship remains to be shown scientifically.

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EXHIBIT 12

Defeating Alzheimer's disease and other dementias: a priority for European science and society



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Executive summary

Alzheimer's disease (AD) is the leading cause of dementia, and because the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically with ageing populations worldwide. Even in high-income countries, the cost of medical care and associated societal burdens of dementia threaten to become overwhelming as more people live into old age. In view of the lack of progress in developing a cure for AD and the rapidly increasing costs of dementia, policy makers and governments have a powerful incentive to provide more resources to develop AD therapeutics. The *Lancet Neurology* Commission was formed with the overarching aim to provide information and expert recommendations to policy makers and political leaders about the growing problem of AD and related dementias of ageing.

The past two decades have seen remarkable improvements in the quality of care for patients with AD, with a research-driven shift to more personalised and integrated team-oriented care. Epidemiological and genetic studies have identified many factors that increase the risk of AD. Prevention studies have highlighted the possibility of targeting risk and protective factors to delay onset, with the promise of reducing the overall prevalence of dementia. However, no treatment is yet available to halt or reverse the underlying pathology of established AD. Indeed, an effective therapy for AD is perhaps the greatest unmet need facing modern medicine. Basic biomedical research has provided insights into the causes and pathogenesis of AD and other neurodegenerative diseases, but improved understanding of disease mechanisms will be needed to develop safe and effective disease-modifying treatments. Nonetheless, several drugs are currently in late phases of clinical development.

The Commission considered a range of challenges that need to be addressed to reduce the burden of dementia, and these challenges are discussed in detail in the main sections of our report: health economics (section 1), epidemiology (section 2), prevention (section 3), genetics (section 4), biology (section 5), diagnosis (section 6), treatment (sections 7, 8), care (section 9), and ethics (section 10). In panel 1 we summarise the key findings of the Commission, with recommendations about how patient care and related research—from basic to clinical—in AD and other dementias should be organised in the future. A concerted effort to tackle dementia is needed, with a substantial overall increase in government and

private investment in the care of patients and the search for AD therapeutics.

Europe is well placed to take the world lead, in partnership with international organisations, to develop new approaches to prevent or cure AD and other dementias and to provide models of compassionate care for patients. As the cost of care increases, funds must not be shunted from basic research, clinical research, and drug-discovery programmes. In fact, a substantial increase in long-term funding for multidisciplinary research programmes is absolutely essential to reduce the burden of individual suffering and the enormous societal cost of AD. Only targeted increases in research investment will provide any hope of finding a cure for AD or developing strategies to delay the onset or slow the progression of the disease.

Introduction

Dementia encompasses a range of neurological disorders characterised by memory loss and cognitive impairment. Alzheimer's disease (AD) is the most common form of dementia, accounting for 50–70% of cases. The most common early symptom of dementia is difficulty in remembering recent events. As the disorder develops, a wide range of other symptoms can emerge, such as disorientation, mood swings, confusion, more serious memory loss, behavioural changes, difficulties in speaking and swallowing, and problems with walking. Progressive accumulation of disability, with deterioration in multiple cognitive domains, interferes with daily functioning, including social and professional functioning.¹ Thus, dementia substantially affects the daily lives of patients, their families, and wider society.

Increasing age is the most important risk factor for AD and other dementias, and as life expectancy increases and demographic ageing occurs in populations around the world, the number of people with dementia is expected to increase. In 2015, almost 47 million people worldwide were estimated to be affected by dementia, and the numbers are expected to reach 75 million by 2030, and 131 million by 2050, with the greatest increase expected in low-income and middle-income countries.² In 2012 and 2015, the World Health Organization (WHO) presented reports in which it acknowledged this trend—sometimes described in terms of a fast-growing epidemic—and concluded that AD and other dementias should be regarded as a global public health priority.^{3,4}

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See [Comment](#) pages 451 and 452

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Panel 1: Key recommendations

Progress in dementia care, treatment, and prevention

- 1 All individuals with Alzheimer's disease (AD) should have access to reliable and timely diagnosis and treatment, irrespective of social inequalities. Accurate and timely diagnosis is a prerequisite for cost-effective care with available interventions. The cost-effectiveness of new therapies will be uncertain when they are introduced and should not be a limiting factor for treatment of this group.
- 2 Guidelines for the provision of dementia care are needed in all countries as part of national policy strategies or national plans. Such frameworks should promote coordination between health-care, social-care, and other relevant sectors (eg, welfare benefits and housing), and include affordable long-term funding plans for dementia care that span these sectors.
- 3 An infrastructure is needed to enable the use of non-pharmacological interventions (eg, psychosocial, behavioural, and environmental interventions, including multidomain approaches) for which clear evidence of benefit already exists. With guidance and advice from public health authorities, evidence-based interventions should be put into practice with appropriate training, support, and maintenance of fidelity.
- 4 Prevention studies need to start in midlife and have a long duration to identify windows of opportunity for effective interventions. Many modifiable risk factors—including high blood pressure, obesity, physical inactivity, and unhealthy diet—are shared among dementias, including AD, and other major late-life chronic disorders, such as heart disease and stroke. Public health efforts to promote healthier lifestyles in midlife have the potential to improve the general health status of the population in old age.
- 5 Available biological markers for AD—including cerebrospinal fluid and brain imaging biomarkers—need to be validated and standardised for use in research and clinical practice, and the search for novel biomarkers with high predictive value at pre-dementia stages needs to be supported and improved. Simple biomarkers (eg, in blood) are needed for use in general practice.
- 6 The discovery of a cure or an effective therapy for AD remains imperative. Ambitious multidisciplinary programmes in basic research are needed to learn more about the causes and pathological mechanisms of AD and to identify new, valid treatment targets.
- 7 Ethical considerations are of increasing importance as diagnosis and treatment shift to earlier disease stages, with a risk of false-positive cases. Important ethical questions need to be addressed in disclosing the genetic status of patients (eg, in families with causal mutations or individuals

with a high risk of AD). At more advanced stages of disease, ethical considerations relate to improved and more timely decision making for end-of-life care.

- 8 Public awareness of AD and other dementias needs to be improved through outreach activities such as public lectures and open-house sessions in clinical care settings, and information provided via mass media, social media, and patient organisations.

Development of an improved infrastructure for research

- 9 Harmonised international databases are needed for population-based longitudinal studies of ageing and dementia to further understand the burden (eg, prevalence, incidence, mortality), natural history (eg, identification of genetic and clinical markers for early detection), and pathogenesis of AD and other dementias (eg, potential contributions of cardiovascular risk factors, nutrition, psychosocial stress, and frailty).
- 10 For optimum use of genetics in pre-symptomatic and early (preclinical or prodromal) diagnoses, current and future treatment approaches, and dementia prevention, DNA and clinical data from epidemiological studies, clinical settings, and clinical trials need to be collected and stored systematically; a legal framework is needed to regulate the use of data for research and to protect affected individuals and their families.
- 11 Scientific collaboration among international research groups demands the development of appropriate infrastructures to enable more effective use of existing data and rapid recruitment of participants in multinational interventional trials. Increased collaboration among governments, and between public and private institutions, will help to accelerate and increase the power of clinical research.
- 12 Redundant research in AD drug development could be avoided by increased openness. Detailed results, outcomes, and databases of clinical trials should be made broadly available immediately after studies have been completed in a manner that is accessible to researchers and the general public.
- 13 Clinical drug development and clinical trials should be coordinated internationally. Budgets for drug discovery, development, and clinical trials should be increased to allow international cohorts, ethical and regulatory frameworks, and standardised methods to be established, which will facilitate clinical trials and accelerate progress.
- 14 Public, private, and corporate funding decisions should be based on evidence and scientific merit, rather than being driven by advocacy, opinion, persuasion, or corporate considerations.

Similar policy declarations have been made by the European Union⁵ (EU) and by some individual countries.

The global economic costs of dementia were estimated to be more than US\$600 billion in 2010,⁶ and \$818 billion

in 2015.² The direct costs of medical and social care, \$487 billion,² represent 0·65% of the aggregated global gross domestic products (GDP)—an enormous economic impact for a single group of disorders, especially given

that 87% of the costs occur in high-income countries. Care for people with dementia is provided by several sectors in society, with the social-care (long-term care and home services) and informal-care (provided by non-professional caregivers) sectors accounting for the greatest proportion of costs—even greater than the cost of direct medical care.⁶ In cost-of-illness studies, total societal cost estimates for dementia in Europe in 2010 were between \$238·6 billion⁶ and €105·6 billion.⁷

The economic costs of caring for a growing number of people with AD and other dementias are formidable, but the combined economic and societal burden of dementia is more daunting still, corresponding to the aggregate burden of people with dementia and their next of kin. No cure or substantial symptom-relieving treatment is available for AD or other dementias, and the progressive nature of dementia can profoundly affect the lives of patients and their families over many years. The impact of this terminal disorder is already enormous, and in view of the predicted rise in prevalence (proportion of the population with the disorder) over the next few decades, AD and other dementias represent a huge challenge for any society.

To tackle the global burden of dementia and its economic and societal ramifications, substantially increased investment in research is needed to accelerate the discovery and development of effective treatments, coupled with a broad, evidence-based public health approach to disease prevention. Progress in understanding the causes and disease mechanisms of AD and other dementias is needed to underpin new diagnostic and therapeutic strategies. Importantly, there is an opportunity and a need to shift the treatment-development paradigm: to establish stronger proof of concept before launching expensive phase 3 trials, to develop multimodal combination treatment approaches, and to allow precompetitive data sharing to accelerate learning and improve the likelihood of success.

At present, awareness about the many challenges of dementia that need to be (and can be) addressed varies substantially among patients and their family members, health-care professionals, politicians, and other stakeholders. It is essential that new knowledge from research is quickly translated into clinical practice and disseminated broadly. In all education programmes, health-care professionals should be made aware of the best available evidence-based care. Our public-sector representatives and policy makers are ultimately responsible for ensuring that clinical and basic research advances are effectively implemented into public health policy. Such an aim demands that our research agenda is broad and engages a wide range of sectors. Policy makers in Europe must support universal access to better diagnosis, care planning, and evidence-based treatment. Simultaneously, European countries must implement disease-prevention programmes and provide incentives for drug development and clinical trials. The overall aim

of this Commission—written by leading health-care professionals representing the areas of health economy, epidemiology, genetics, biology, diagnosis, treatment, care, and ethics—is to inform, guide, and stimulate public debate about the growing burden of dementia in Europe, with a focus on AD as the leading cause of dementia.

Section 1. Health economics of Alzheimer's disease

AD has a substantial economic impact for each person and family affected. A 2011 study⁸ of a multinational (Spain, Sweden, the UK, and the USA) sample of 1222 patients estimated that societal costs amount to about €14·500 per year in patients at home with a high level of autonomy in activities of daily living (ADL), but rises up to €72·500 per year in patients who need residential care. In 2014, the direct cost of AD for payers in the USA alone was estimated to be \$214 billion.⁹ For comparison, the global direct cost (resources used for prevention and treatment) and indirect cost (resources lost owing to morbidity or mortality, such as lost work productivity) of cancer was estimated at \$290 billion in 2010, the estimate for diabetes was \$472 billion, and that for all cardiovascular disease (including cerebrovascular disease) was \$863 billion.¹⁰

For diabetes, the direct costs amounted to 80% of the global economic burden of the disease (almost 90% in high-income countries) in 2010. Thus, indirect costs constituted a small proportion of the overall economic burden.¹⁰ These substantial direct costs reflect the availability of effective medical therapy to manage glucose control, prevent complications when possible, and treat complications when they occur. By contrast, only 16% of costs for AD were direct medical costs, 41·7% were informal-care costs, and 42·3% were social-care costs (section 9).¹⁰ Thus, the costs of AD are driven mainly by compensating for lost function rather than treatment or prevention. The entire global market for pharmaceuticals and diagnostics for AD was estimated to be \$10 billion in 2015, or roughly 1% of the total costs of the disease.¹¹ This highlights not only the absence of effective therapy for AD (section 7), but also the opportunity for new treatment options to provide benefit by improving health outcomes and shifting from indirect to direct costs.

Costs of diagnosing AD

Insufficient diagnostic services remain a major barrier to the provision of appropriate care for patients with dementia. Although disease-modifying treatments are not available at present, timely and correct diagnosis is a prerequisite for access to support services (eg, help with living arrangements) and symptomatic treatment (sections 6–9).

It is estimated that only 20–50% of patients living with dementia have a documented diagnosis in primary care, and this proportion is substantially lower in low-income and middle-income countries.¹² On the basis of data from the Swedish Dementia Registry (SveDem), the average

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cost of diagnosing a case of AD in primary care was estimated to be €753, whereas the corresponding cost in specialist care was €1298 in 2010.¹³ Table 1 presents an example from Sweden of the costs involved in diagnosing

	Unit cost (€)	Cumulative cost (€)
Primary care		
Visit to family physician	122	122
Routine blood tests	33	156
CT	200	356
Visit to occupational therapist	144	500
Specialist care		
Visit to specialist physician	367	867
Neuropsychological testing	422	1289
EEG	100	1389
CSF tests	622	2011
MRI	289	2300
SPECT	378	2678
PET	1711	4389
Analyses of amyloid markers	1166	5555

According to level of primary and specialist care, and cumulative cost as each new diagnostic procedure is added.¹³ Costs in Swedish kronor have been converted to euros on the basis of the exchange rate €1=9kr. Figures are rounded to the nearest euro. CT=computed tomography. EEG=electroencephalography. CSF=cerebrospinal fluid. MRI=magnetic resonance imaging. SPECT=single-photon emission computed tomography. PET=positron emission tomography.

Table 1: Costs of diagnosing a case of Alzheimer's disease

a case of AD, and a calculation of the cumulative costs as each new diagnostic procedure is added, starting in primary care and transitioning to specialist care.¹³ Even though the maximum diagnostic cost (assuming all available diagnostic procedures are done) is more than €5000, which is high compared with the costs of diagnosing other common chronic disorders for which diagnostic biomarkers are available (eg, diabetes), this cost would be only a small fraction of the lifetime costs of care incurred by a patient with AD.

The economic costs for individuals with dementia who remain undiagnosed are largely borne by caregivers and by patients themselves. With the possible future availability of effective treatments, early identification of AD pathological changes becomes even more important. The cost-effectiveness of treatment will ultimately depend on the strategy for identification of patients eligible for that treatment.

Indirect and intangible costs of AD

Methodological challenges exist in measuring the costs of informal care for patients with AD, both in the estimation of the amount of time spent caring for a patient and in how this time should be valued. Studies have suggested that caregivers would be prepared to pay between £59 and £144 per hour, depending on the country of study, for reductions in the time spent on caregiving tasks.¹⁴ In addition to the direct and indirect economic costs of AD, the associated burden of illness includes the intangible costs of reduced quality of life and mortality. In health-economic evaluations, these costs are often quantified in terms of quality-adjusted life years (QALYs; panel 2).

Health utility weights for disease states in AD (panel 2) calculated with the Health Utilities Index (in which 1 equals perfect health and 0 is equivalent to death) range from 0.69 in mild disease to 0.14 in severe disease.¹⁵ Using a different instrument, EuroQoL's EQ-5D, weights have been estimated as ranging from 0.69 in mild dementia to 0.33 in severe dementia.¹⁶ For comparison, the population mean health utility weight in the age group 65–74 years is 0.78 and the utility weight for legal blindness has been estimated as 0.26.¹⁷ DEMQoL is an instrument that, unlike the Health Utilities Index and the EQ-5D, was specifically developed to measure quality of life in dementia, and a tariff linking responses on the DEMQoL to health utilities has been developed.¹⁸ Most studies have relied on proxy assessments of the health status of patients with AD. The agreement between patient and proxy ratings with the EQ-5D and DEMQoL has varied across studies; however, agreement is generally poorer in severe disease states. The quality of life of caregivers themselves can also be affected. Studies have shown an increased prevalence of depression in caregivers of patients with AD.¹⁹ However, no direct link between caregiver health utilities and the severity of dementia in the patient whom they care for was noted using the

Panel 2: QALYs and DALYs explained

One quality-adjusted life-year (QALY) corresponds to a year spent in perfect health. Years spent in less than perfect health states (eg, with Alzheimer's disease) are assigned a weight (health utility), calculated on the basis of preferences for the health state. A weight of 1 signifies perfect health, whereas a weight of 0 means that the health state is equivalent to death. Weights below 0 are also theoretically possible (ie, a health state worse than death).

The disability-adjusted life year (DALY) is a construct that, like the QALY, summarises morbidity and mortality in terms of a single index. The number of DALYs is calculated as:

$$\text{DALYs} = \text{YLL} + \text{YLD}$$

YLL is years of life lost—an estimate of the average years a person would have lived if he or she had not died prematurely. The formula for YLL (without including social preferences) is:

$$\text{YLL} = N \times L$$

N is number of deaths in a particular population and L is the standard life expectancy at age of death (in years) for that population.

YLD is years of life with disability. To estimate the YLD for a particular disease over a specific period, the number of incident cases in that period is multiplied by the mean disease duration (until remission or death) and a disability weight reflecting the severity of the disease on a scale from 0 (perfect health) to 1 (dead). The basic formula for YLD (again, without applying social preferences) is:

$$\text{YLD} = I \times \text{DW} \times L$$

I is the number of incident cases, DW is disability weight, and L is the average duration of disease.

EQ-5D.¹⁶ More specific and sensitive instruments are needed to measure the potential disutility associated with caregiving.

WHO has estimated the disability weights (where 0 equals no disability and 1 equals complete disability) in AD and other dementias as 0·082 for mild dementia, 0·346 for moderate dementia, and 0·438 for severe dementia.²⁰ In 2012, AD and other dementias were estimated to be the cause of 18 million disability-adjusted life years (DALYs) globally—years lost because of ill health, disability, or early death (panel 2). This is just 0·7% of all DALYs; however, in European women aged 70 years or older, AD causes 6% of DALYs.²¹

Valuing each DALY at three times the gross domestic GDP per person, the intangible cost of illness of AD and other dementias is around \$550 billion (table 2).²² Thus, the intangible cost of dementia might be almost as high as the total direct and indirect costs of care for AD.

Current challenges and future goals

New treatment modalities and strategies for prevention and care will be key to reversing the increasing prevalence (and associated morbidity) of AD (section 2). As new options for diagnosis and treatment become available (sections 6, 7), they will undergo two stages of assessment, the first by regulatory agencies to determine risk and benefit, and the second by health technology assessment (HTA) agencies and payer organisations to determine value relative to the current standard of care and to inform coverage and reimbursement decisions. Tools are needed that allow determination of the value of these new technologies with a sufficient degree of certainty to make correct coverage decisions. If a new treatment receives regulatory approval but faces negative reimbursement decisions owing to inadequate demonstration of value, uptake of the new treatment will be low and patients and caregivers will miss out on potential treatment benefits.

An important issue in establishing the value of new treatments for AD is that the benefits will largely fall outside the health-care sector, because most of the potentially preventable costs of dementia relate to long-term care and burden on informal caregivers. Increasing availability of treatment options with the potential to change the long-term course of AD will probably necessitate substantial upfront investments in diagnosis and medical expenditure, at least in the short term, and the full benefits could take years or decades to be realised. The benefits of reducing the need for informal caregiving will not appear on any budget and cannot easily offset treatment costs. Furthermore, for funding decisions a short time horizon is sometimes used or discounting applied, such that the value of future costs and effects is decreased (relative to current costs and effects) to reflect negative time preferences. Although it is common for budgeting constraints to prevent the flow of funds between so-called silos—eg, savings made through reduced need for long-term care being used to finance increasing costs

	Total DALYs (millions)	DALYs due to AD and other dementias (millions)	Proportion of DALYs due to dementia (%)	GDP per person (US\$)	Intangible cost (US\$ billion)
World	1523	11·16	0·7%	...	550
High income	122	4·39	3·6%	38 182	503
Upper-middle income	121	1·04	0·9%	7289	23
Lower-middle income	452	3·73	0·8%	1924	22
Low income	828	2·00	0·2%	596	4

Data obtained from the World Bank. Intangible costs are valued at three times the GDP per person per DALY. DALY=disability-adjusted life year. AD=Alzheimer's disease. GDP=gross domestic product.

Table 2: DALYs due to, and intangible cost of, Alzheimer's disease and other dementias in world regions according to World Bank income level

of drug therapy—it is crucial that the long-term value of investment in medical care is recognised.

The main value of therapies that affect the long-term course of disease will lie in shortening the time spent in the severe stages of dementia. However, because this outcome is not being studied in trials of new drugs, value will need to be estimated through forecasting models before treatments are even introduced in clinical practice. The accuracy of such models depends on the availability of long-term, high-quality data for disease progression rates, costs, and health outcomes. Several epidemiological studies have followed up patients with AD longitudinally from diagnosis until the end stages (eg, the Swedish National Study on Aging and Care [SNAC]²³ and the European Alzheimer's Disease Consortium–Impact of Cholinergic Treatment Use [EADC-ICTUS]²⁴ studies). Far fewer data are available from the very early phases of AD, before the onset of dementia. New therapies are being assessed in preclinical states of dementia, and thus new data sources are needed to model accurately the long-term benefits of these treatments.

Results from economic models are highly contingent on assumptions about long-term treatment benefits that will not be immediately available from clinical trials. For instance, the potential impact of treatment on overall mortality has important implications for costs of care.²⁵ If treatment improves survival but prolongs the time spent with severe dementia, it might bring only marginal health benefits for patients but increase care costs substantially. However, if late-stage morbidity is compressed and patients spend proportionally more time in less severe states, cost savings could be substantial. Thus, the goal of therapy is not merely to slow disease progression, but to minimise the time spent with severe dementia and maximise the time with conserved cognitive resources, autonomy in ADL, and quality of life.

Patients who receive new therapies will need to be followed up in clinical practice, and data will need to be gathered for resource use and health outcomes to gain further understanding of the value provided as new treatment options are implemented. Few countries have the infrastructure available at present to follow up patients prospectively, as can be done through SveDem.¹³

For more on the European Alzheimer's Disease Consortium see <http://www.eadc.info/>

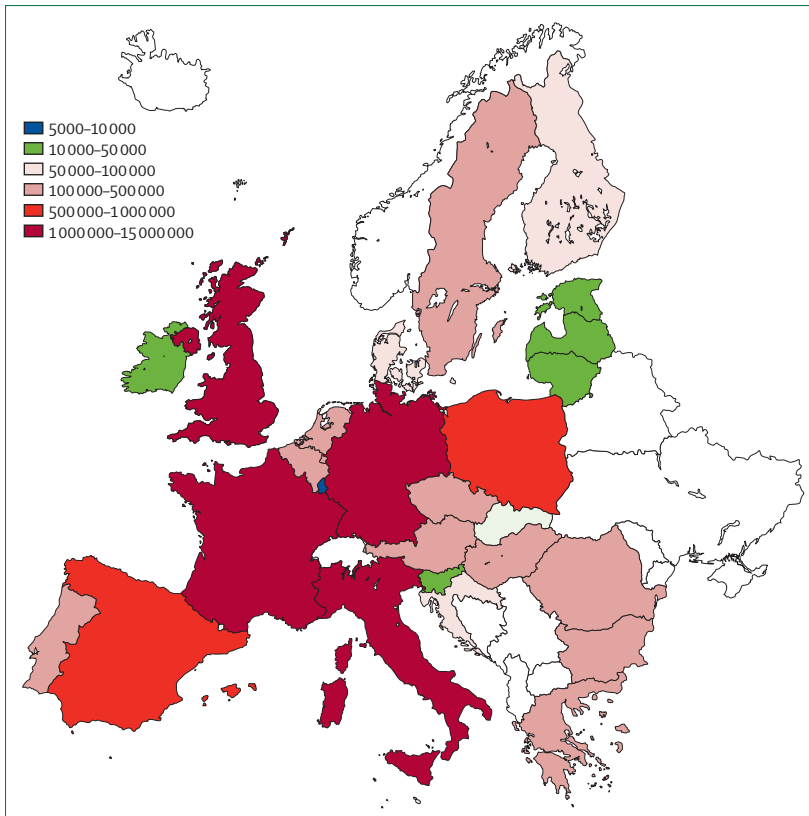


Figure 1: Number of people with dementia in 28 European countries in 2013
Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe.²⁶

Furthermore, data collected might not immediately be relevant for other countries because of international differences in care organisation and delivery. Observational studies, such as EADC-ICTUS, in which data are gathered across several countries will be an important addition.

Summary and recommendations

The societal costs of AD will increase substantially as global prevalence increases. Despite some evidence of a decrease in incidence (the number of individuals who develop a disorder during a particular period) in Europe and the USA, a substantial increase in prevalence seems unavoidable as people live longer. At present, only about 16% of costs associated with AD are direct (related to resources used for prevention and treatment); most costs are indirect, including care and societal costs. New approaches to diagnose and treat AD should be assessed in the context of new paradigms for cost-benefit analysis to optimise the use of resources and improve quality of life for patients with AD.

(1) Economic assessments of new methods to diagnose and treat AD should include all costs of the disorder and adopt a broad measure of outcome that captures full societal benefits of treatment.

(2) The aim should be to offer accurate, reliable, and timely diagnosis to patients to provide cost-effective care with available therapies and to realise the potential value of new disease-modifying therapies.

(3) The cost-effectiveness of new therapies will be uncertain when they are introduced, because experience of long-term benefits will be limited, whereas upfront treatment costs can be substantial. Follow-up with data collection in clinical practice on resource use and patient-relevant outcomes should be done routinely to facilitate the assessment of treatment benefits and cost-effectiveness in clinical practice.

Section 2. Epidemiology of Alzheimer's disease and dementia

The burden of AD and other dementias, which is projected to surge in the coming decades, poses a serious threat to the sustainable development of economies and the social welfare systems of Europe. Epidemiological studies generate knowledge about the occurrence (eg, prevalence and incidence), distribution (eg, demographic, geographical, and temporal variations), determinants (eg, genetic and non-genetic risk or protective factors), health economics (eg, costs of health care and cost-effectiveness of treatment and intervention), and intervention strategies (eg, therapeutic and preventive interventions) of AD and other dementias. Such studies are therefore key to understanding and tackling the challenges of this devastating disorder. In EU countries, knowledge about the number of people with dementia is available, but fewer data have been reported on the prevalence of dementia in eastern European countries (figure 1).²⁶ To cope with the challenges of AD and other dementias, policy makers need this information, which will help to guide the design and development of care and social welfare systems, and allow appropriate use of scarce resources for the care of people with dementia. Specialist terms that are key to our discussion are defined in panel 3.^{27,28}

Although AD diagnosed by current clinical criteria (section 6) accounts for 50–70% of all dementia cases, autopsy-verified studies have suggested that mixed dementia, with vascular and neurodegenerative AD pathology, accounts for most dementia cases. Additionally, AD with onset before age 65 years (early-onset AD) accounts for up to 5% of all cases. Most of the early-onset AD cases are familial AD—a rare form of AD caused by mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or PSEN2 genes (section 4).²⁹ Patients with non-familial (sporadic) early-onset AD have no reliable family history and usually have an older age of onset than do patients with familial early-onset AD.³⁰ Late-onset sporadic AD (from 65 years of age) is the most common form of AD, accounting for about 95% of all cases. The enormous costs of medical and social care for patients with early-onset and late-onset AD depend on

Panel 3: Definitions

Allele: any of the alternative genetic variants of a specific gene or locus.

Attributable fraction of risk: the fraction of cases that would be avoided if a risk factor could be totally suppressed.

Autosomal dominant: a mode of inheritance in which a single copy of a mutant allele located on one of the 22 pairs of autosomes (non-sex chromosomes) is sufficient to cause a disease. In diseases with mendelian autosomal dominant transmission, which does not depend on the sex of the carrier parent, each child of an affected parent has a one in two (50%) risk of inheriting the disease.

Brain reserve: the brain's ability to tolerate age-related or disease-related pathology before the threshold is reached for clinical symptoms to appear. Brain reserve is directly related to brain size, number of neuronal cells, or density of synapses, such that a large brain or large number of cells is able to tolerate more pathology.²⁷

Cerebral small vessel disease: a cerebrovascular disease characterised by a range of neuroimaging, pathological, and associated clinical features. Signs of cerebral small vessel disease on conventional magnetic resonance imaging (MRI) scans include small subcortical infarcts, white matter hyperintensities, lacunes, prominent perivascular spaces, and cerebral microbleeds.²⁸

Codominance: an additive relation between variants of one gene (alleles), in which an increased effect on phenotype is noted with increasing number of alleles (ie, two copies of the allele result in a more severe phenotype than one copy of the allele).

Cognitive reserve: the brain's ability to perform cognitive tasks adequately despite neuropathological damage to the brain. Cognitive reserve represents an enhanced ability to use brain networks more efficiently or to recruit alternative networks. It is associated with high education, mentally stimulating activity, physical and mental leisure activities, and rich social networks.²⁷

Cognitive stimulation: an intervention for people with dementia that offers various interactions and activities that are designed to keep the brain active. The notion that cognitive stimulation is beneficial for people with dementia is based on the use-it-or-lose-it philosophy.

Confounder: a factor related to both an exposure of interest and an outcome (eg, a disease). The factor (confounder) might explain all or part of an association between an exposure and an outcome; a spurious relation between exposure and outcome might be inferred if the confounder is not taken into account.

Delphi consensus: a structured method to achieve expert consensus. Experts answer several iterations of questions, with a facilitator providing an anonymous summary of the experts'

forecasts from the previous round and the reasons they provided for their judgments. Through discussion and reconsideration of their answers to the stated questions, a consensus is achieved.

Epigenetic modifications: variations in genetic make-up that do not include the DNA sequence (code) itself, such as DNA methylation (methyl groups added to the nucleotide cytosine) and modification (eg, acetylation) of proteins that bind to the DNA. Such variations, which can be heritable, make the DNA more or less accessible for activation (transcription).

Implicit memory: an aspect of memory in which previous experiences help with the performance of a task even though there is no conscious awareness of these experiences.

Life-course approach: in epidemiology, a life-course approach is used to study the biological, physical, and social hazards during gestation, childhood, adolescence, young adulthood, and midlife that might affect risks for chronic diseases and health outcomes in later life. The approach aims to identify the underlying biological, behavioural, and psychosocial processes that operate across the lifespan.

Locus: in genetics, a locus is a specific location or position of a gene or DNA sequence on a chromosome, analogous to the specific coordinates of a geographical location on a map.

Mediterranean diet: a modern nutritional recommendation based on traditional dietary patterns of the Mediterranean region. Key components of the diet include olive oil, vegetables, and fish, with moderate consumption of dairy products (mostly as cheese and yoghurt) and low consumption of meat products.

Minor allele frequency (MAF): the frequency of the less common allele (genetic variant) in the population. The term usually refers to the less common of two different alleles of a single-nucleotide polymorphism.

Population attributable risk (PAR): the proportion of cases that would not occur in a population if a factor were completely eliminated from the population. The PAR or population attributable fraction (%) in a population depends on the prevalence of the risk factor (P_e) and the strength of its association (relative risk) with the disease (RR_e). The formula is:

$$PAR = \frac{P_e (RR_e - 1)}{[1 + P_e (RR_e - 1)]}$$

Precision medicine: an approach to health care, also known as personalised medicine, in which choices for treatment and prevention are tailored to the individual. When a trait or disease is influenced by genetic make-up, health-care decisions can potentially be made on the basis of the specific genetic background of the individual (ie, genomics). The notion can be extended to transcriptomics, proteomics, metabolomics, and so on.

(Panel continues on next page)

The Lancet Neurology Commission

(Panel 3 continued from previous page)

Reality orientation: a programme designed to improve cognitive function in people with dementia. The aim is to use verbal interaction, aids such as calendars and clocks, and sensory stimuli such as distinctive sights, sounds, and smells to improve orientation and sensory awareness.

Reminiscence therapy: a therapeutic approach in which tools such as life histories, shared memories, and familiar objects from past periods are used to improve wellbeing, usually in a group setting.

Single-nucleotide polymorphism (SNP): a genetic variation in a single-nucleotide base pair. The DNA sequence (code) of the human genome is made up of billions of nucleotide base pairs. Generally there are two alleles for each SNP.

Somatic mutation: acquired genetic variation that occurs during cell division (mitosis) in the cells of the body and is not transmitted to the next generation because for trans-generational transmission the mutation has to be present in the gonadal cells.

disease severity (section 1);³¹ however, prevalence data of dementia according to severity or stage are scarce.^{32,33}

Living with dementia

Several population-based studies have suggested that people aged 65 years or older survive a median of 3–9 years after a diagnosis of dementia, with some living for as long as 20 years.^{34–42} Clinical deterioration of people with dementia, and particularly of people with AD, is progressive, although the rate of decline in mental and physical function can vary. According to WHO, people can generally expect to be in the mild or early stage of dementia (eg, forgetful, some language difficulties, and mood changes) for the first year or two, the moderate or middle stage (eg, very forgetful, increasing difficulty with speech, and help needed with self-care activities) from the second to the fourth or fifth years, and the severe or late stage (eg, serious memory disturbances and nearly total dependence and inactivity) from the fifth year onwards.³ Data from the Kungsholmen Project of community dwellers aged 75 years or older in central Stockholm showed that people with incident dementia (ie, cases newly diagnosed during the study) spend a few months in the very mild stage of dementia, around 2 years in the mild phase, 1–2 years in the moderate stage, and a year in the severe stage.⁴³

Women with dementia live longer than men, because they tend to survive longer in the severe stage.^{43,44} More than 50% of dementia cases are estimated to reach the severe stage within 3 years. A population-based study⁴⁵ of prevalent dementia cases (ie, those diagnosed at the start of the study) showed an increase in the proportion of severe dementia from 19% at baseline to 48% after 3 years, and 78% after 7 years. By contrast, in a population-based prospective study⁴⁶ of dementia progression (Cache County), 40–50% of patients with incident AD deteriorated slowly in cognitive and functional ability (eg, a decline of 1 point per year on the Mini-Mental State Examination [MMSE] score and the Clinical Dementia Rating Sum of Boxes). Although several studies have been done,^{45,47–50} the effect of cognitive decline on specific tasks of self-care ADL (eg, eating, dressing, toileting) or instrumental ADL (IADL; eg, shopping, cooking, basic housework) has still

not been completely clarified, largely as a result of the short periods of follow-up for most studies.^{51–53} Furthermore, knowledge about the effect of potential compensatory factors (eg, social engagement, cognitive training, and mentally stimulating activity) is still poor.

In many countries, health-care policy aims to avoid or postpone admission of patients with dementia to nursing homes and institutions. Informal care (eg, home care provided by family and friends) tends to be less costly than formal care (eg, care provided in nursing homes or institutions) for the social security system,⁵⁴ although this is not necessarily true when the costs are assessed from a societal perspective.⁵⁵ In addition to health-care and social-care policies, the proportion of people with dementia living at home depends on several factors, including the characteristics of patients (eg, severity of cognitive and functional disability) and caregivers (eg, perceived burden and coping strategies), and cultural factors.

Worldwide, most people with AD and other dementias are cared for at home, usually by a spouse or a daughter. In low-income and middle-income countries, the estimated proportion of people with dementia living at home is around 94%, compared with around 66% in high-income countries.⁵⁶ The proportion of people with dementia cared for at home is higher in rural than in urban areas.⁵⁷ A longitudinal study in Australia showed that several baseline clinical features of dementia predicted a shorter time before admission to an institution, such as lower cognitive and functional ability, more neuropsychiatric symptoms, and use of antipsychotic drugs.⁵⁸ Moreover, greater deterioration in these factors within the first 3 months after baseline was also predictive of shorter time to admission to an institution, which suggests that rate of disease progression is an important factor.

Dying with dementia

Several follow-up studies have consistently shown that the extent to which dementia shortens life expectancy depends on age at onset, sex, and dementia subtype.⁴⁴ Data from the UK Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) showed that the prevalence of dementia and severe cognitive

For more on the Kungsholmen Project see <http://www.kungsholmenproject.se/>

For more on the Cognitive Function and Ageing Studies see <http://www.cfes.ac.uk/>

impairment in the period before death rises steeply with age; by age 90 years, around 60% of people died with dementia or severe cognitive impairment.^{59,60} Finally, not only dementia shortens life expectancy: a subtle decrement in global cognitive function, even in the absence of clinically recognised impairment, is also strongly associated with shorter survival.⁶¹

The potential years of life lost (YLL)—ie, the average number of additional years a person would have lived if he or she had not died prematurely—because of dementia in people aged 75 years or older has been estimated at 3–5 years.^{43,44} A Swedish study of people aged 75 years or older suggested that the impact of dementia on lifespan (YLL 3.41) is similar to that of cardiovascular disease (YLL 3.58) but lower than that of cancer (YLL 4.40).⁴³ Mortality risk in patients with dementia or cardiovascular disease is twice as high as that of people without these disorders, whereas patients with a diagnosis of cancer have a mortality risk three times higher than that of people without cancer.⁴³ Furthermore, the estimated years lived with or lost because of one of these disorders is most dependent on age at diagnosis, being higher among the younger old (those aged 75–84 years) than in the oldest old group (85 years or older; figure 2).⁴³ This finding is supported by a 2014 study in the USA showing that the mortality risk for AD was higher for younger old participants than for the oldest old participants (relative risk 4.30 vs 2.77; $p < 0.05$).⁶²

AD and other dementias are substantially under-reported on death certificates and medical records, although the situation has improved in the past 20–30 years as a result of increasing awareness of the disease among health professionals and the public. The contribution of dementia to mortality is difficult to assess solely on the basis of death certificates, because dementia is rarely thought of as an immediate or an underlying cause of death in this context.⁶³ Indeed, older people often have different chronic and acute illnesses that might be related to the dementia process⁶⁴ and a direct or indirect cause of death. A population-based study estimated that the population attributable risk (%) of death owing to AD was about 36% for people aged 75 years or older, and that in the USA, AD might contribute to almost as many deaths as does heart disease or cancer.⁶² Similarly, in a US nationwide study of individuals aged 65 years or older, deaths with AD were estimated to comprise 32% of all deaths in 2010, with the proportion projected to reach 43% by 2050.⁶⁵ In 2013, the US Alzheimer's Association reported that AD was the sixth leading cause of death across all ages, and the fifth leading cause of death for people aged 65 years or older in the USA.⁶⁶ In the UK, the rank (among all other diseases) of the age-standardised YLL for AD increased from 24th in 1990, to 10th in 2010.⁶⁷ When death with dementia is examined, the proportion of deaths attributable to dementia reached around one-third in people aged 85 years or older.⁶⁸

Temporal and geographical variations

The age-standardised prevalence of dementia for people aged 60 years or older is 5–7% in most regions of the world. In the past decade, the work of the 10/66 Dementia Research Group has contributed to understanding of the epidemiology of dementia in low-income and middle-income countries, such as Brazil, India, and China.^{69–71} Systematic reviews and meta-analyses provide more precise global and regional estimates of dementia prevalence.^{3,5,72,73} They also show similar patterns of age-specific prevalence of AD and dementia across worldwide regions, although substantial variations are evident among the oldest old (90 years or older; figure 3).^{72–75} Higher prevalence and incidence of dementia and AD in women than in men, especially among the oldest old,

For more on the 10/66 Dementia Research Group see <http://www.alz.co.uk/1066/>

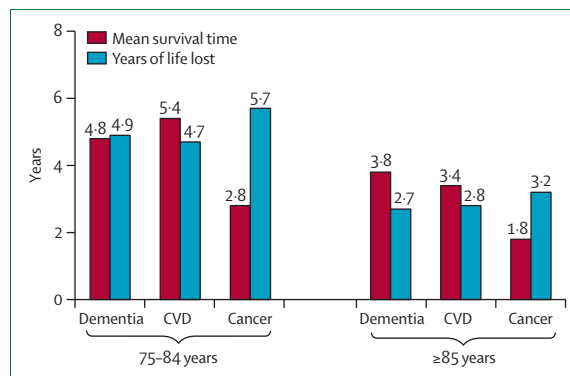


Figure 2: Mean survival time and years of life lost to dementia, cardiovascular disease, and cancer

Data are stratified by two age groups.⁴³ In people aged 75 years or older, the effect of dementia on lifespan is similar to that of CVD, but lower than that of cancer. Years of life lost is an estimate of the average additional years a person would have lived if he or she had not died prematurely. It is an alternative to death or mortality rates, but gives more weight to deaths that occur among young people. Years of life lost can be estimated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs. CVD=cardiovascular disease.

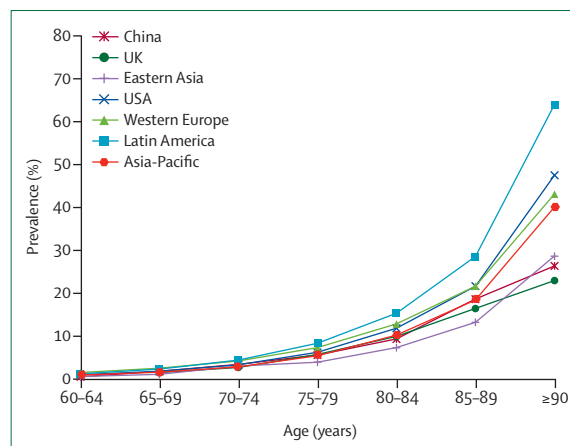


Figure 3: Age-specific prevalence of dementia by world region and in major countries

Patterns of age-specific prevalence of dementia are similar across worldwide regions, but vary substantially among the oldest old (age ≥90 years).^{72–75}

For more on the Alzheimer's Association see <https://www.alz.org/>

have been reported in several studies in Europe and Asia, although data about sex differences have been less consistent in North American studies.⁷⁶

Study of the secular trends and geographical variations of dementia occurrence and their determinants is crucial for policy development in a world that faces a rapid increase in the absolute number and proportion of older adults in the population. Thus, there has been increasing interest in investigating the time trends of dementia occurrence (eg, incidence and prevalence; table 3)^{68,77–92} and possible geographical differences in dementia distribution in the past few years.⁷⁴ Although findings from various regions across the world have not been consistent, the results of several population-based community surveys point to a stable or declining age-specific prevalence or incidence of dementia among elderly people in Europe and North America.^{93–95} Identification of temporal and geographical variations in the prevalence and incidence of dementia will help to establish modifiable risk and protective factors for dementia disorders, and could help to shape public health policy in Europe and elsewhere.

North America

A decline in the prevalence of dementia and cognitive impairment has been reported in a few studies from the USA,^{77,96,97} and another study suggested a stable age-adjusted prevalence of dementia and AD in African American people aged 70 years or older from 1992 to 2001.⁷⁸ Additionally, several population-based studies from the USA have shown a decline (2–3% per annum) in the incidence of dementia and AD from the 1990s through the 2000s.^{79,80} More recently, two studies from the USA provide direct evidence supporting the declining trend of age-specific incidence of dementia starting even from the 1970s.^{81,82}

Europe

Two population-based surveys^{68,85} in Sweden showed a stable age-specific prevalence of dementia over the past 20–30 years. Repeated cross-sectional surveys⁸³ in 1988 and 1994 in Spain suggested an age-standardised stable prevalence of dementia in women but a decreased prevalence in men. Finally, the large-scale MRC CFAS study⁸⁶ provided evidence that a cohort effect might exist in the age-specific prevalence of dementia among community residents, such that later-born populations had a lower likelihood of prevalent dementia than those born earlier in the past century, whereas the prevalence of dementia among older people living in care settings increased. However, the study showed no evidence of variations in the incidence or prevalence of dementia across five regions in England and Wales. A systematic review⁷⁴ revealed evidence of geographical variations in the incidence or prevalence of dementia and, specifically, a higher risk of AD in rural as opposed to urban areas. Studies from the Netherlands, Sweden, and England have also provided evidence suggesting a declining

incidence of dementia among community-dwelling older people.^{68,84,86} Given the diversity in social service systems and economic development across Europe, epidemiological studies of dementia and AD in eastern and middle European countries are needed.^{98,99}

Asia-Pacific region

In mainland China, the prevalence of dementia and AD increased steadily across all age groups of people aged 55 years or older from the 1990s to 2010,⁸⁹ although the reported trends might be attributable partly to methodological variations during the periods of study (eg, diagnostic criteria, age range, and sampling methods).⁹⁰ The number of people with dementia was estimated to have increased by 63·5% from 2000 to 2010 in China—compared with an average increase of 46·5% worldwide during almost the same period^{172,73}—largely owing to the fast pace of population ageing in China. Rural and urban differences in the prevalence of dementia and AD are supported by a large-scale study from China,¹⁰⁰ which suggested that early experience of, or exposure to, rural living (with low education and socioeconomic status) might contribute to the association between rural life and an increased risk of late-life dementia and AD. In Hong Kong, a systematic review⁸⁸ showed that the prevalence of clinically diagnosed dementia among community-dwelling people aged 70 years or older increased from 4·5% in 1995, to 9·3% in 2005–06. In Japan, the population-based Hisayama study⁹¹ suggested that the age-specific prevalence of all-cause dementia and specific AD significantly increased from the early 1990s to 2005 in a general population of elderly people. After all methodological variations were carefully assessed, an increasing prevalence of dementia in Japan was confirmed by a systematic review.⁹² These findings suggest that previous estimates of dementia burden and long-term trends in dementia occurrence across the world, especially in the Asia-Pacific region, were probably underestimates.¹⁰¹

Determinants of temporal and geographical variations

Many factors can affect estimates of the occurrence of dementia, so it is no surprise that temporal trends vary within and between countries. For instance, the upward trend in the prevalence of dementia from the 1990s to 2010 in China is consistent with the time trends for increasing prevalence of stroke and ischaemic heart disease, and related lifestyle and metabolic risk factors (eg, smoking, physical inactivity, obesity and overweight, hypertension, diabetes), over similar periods,¹⁰² together with a fast pace of population ageing in China. Similarly, a substantial reduction in the prevalence of dementia in England from 1991 to 2011, and the suggested reduction of dementia risk in the Netherlands and Sweden, imply that changes in health behaviours (eg, smoking cessation, physical activity), improved management of cardiovascular risk factors (eg, hypertension, high cholesterol), and reduced

	Study design	Study population and period	Outcome (diagnostic criteria)	Findings
North America				
Langa et al, 2008 (USA) ⁷⁷	Repeated surveys in the Health and Retirement Study	Age ≥70 years for both waves: wave 1 (1993; n=7406), wave 2 (2002; n=7104)	Prevalence of cognitive impairment (≤10 on 35-point cognitive scale)	Prevalence decreased from 12.2% to 8.7%
Hall et al, 2009 (Indiana, USA) ⁷⁸	Repeated cross-sectional surveys	African Americans ≥70 years: wave 1 (1992; n=1500), wave 2 (2001; n=1892)	Prevalence of dementia and AD (ICD-10)	Prevalence stable for dementia (6.75% to 7.45%) and AD (5.47% to 6.77%)
Hebert et al, 2010 (Chicago, USA) ⁷⁹	Repeated cross-sectional surveys every 3 years	Age ≥65 years for all cycles (1997–2008; n>10 000): cycle 1 (n=6158)	Incidence of AD (NINCDS–ADRDA)	Risk of AD stable over time (OR for trend variable 0.97, 95% CI 0.90–1.04)
Rocca et al, 2011 (USA) ⁸⁰	Review	1993–2002	Prevalence or incidence of dementia and AD (DSM–III–R, DSM–IV, NINCDS–ADRDA, ICD–10, others)	Prevalence and incidence stable
Gao et al, 2015 (Indiana, USA) ⁸¹	Repeated surveys in the Indianapolis-Ibadan Dementia Project	African Americans ≥70 years: 1992 cohort (n=1440), 2001 cohort (n=1835)	Incidence of dementia (DSM–III–R) and AD (NINCDS–ADRDA)	Age-standardised annual incidence rate declined from 1992 to 2001 for dementia (3.6% [95% CI 3.2–4.1%] vs 1.4% [1.2–1.7%]) and AD (2.5% [2.1–2.9%] vs 1.3% [1.0–1.5%])
Satizabal et al, 2016 (Boston, USA) ⁸²	Repeated surveys in the Framingham Heart Study	Age ≥60 years: epoch 1 (1977–83; n=2457), epoch 2 (1986–91; n=2135), epoch 3 (1992–98; n=2333), epoch 4 (2004–08; n=2090)	Incidence of dementia (DSM–IV), AD (NINCDS–ADRDA), and vascular dementia (NINDS–AIREN)	Decline in incidence rate per decade of 20% (95% CI 10–28%) for dementia, 12% (0–23%; p=0.052) for AD, and 29% (10–44%) for vascular dementia
Europe				
Lobo et al, 2007 (Spain) ⁸³	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1988–89; n=1080), wave 2 (1994–96; n=3715)	Prevalence of dementia (DSM–IV)	Prevalence stable overall (5.2% to 3.9%) and decreased in men (5.8% to 2.3%)
Schrijvers et al, 2012 (Rotterdam, Netherlands) ⁸⁴	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1990; n=5727), wave 2 (2000; n=8384)	Incidence of dementia (DSM–III–R)	Incidence decreased, but not significantly (age-adjusted IRR 0.75, 95% CI 0.56–1.02; p=0.06)
Qiu et al, 2013 (Stockholm, Sweden) ⁶⁸	Repeated cross-sectional surveys	Age ≥75 years for both waves: wave 1 (1987–89; n=1700), wave 2 (2001–04; n=1575)	Prevalence and survival of dementia (DSM–III–R)	Prevalence stable (17.5% to 17.9%); evidence suggests decline in incidence
Wiberg et al, 2013 (Gothenburg, Sweden) ⁸⁵	Repeated cross-sectional surveys	Wave 1 (1976–77; age=70 years, n=404; age=75 years, n=303), wave 2 (2000–01; age=70 years, n=579; age=75 years, n=753)	Prevalence of dementia (historical criteria in wave 1; DSM–III–R in wave 2)	Prevalence stable (70 years, 2.0% to 2.4%; 75 years, 5.0% to 6.0%)
Matthews et al, 2013 (England) ⁸⁶	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1989–94; n=7635), wave 2 (2008–11; n=7796)	Prevalence of dementia (Geriatric Mental State scale)	Prevalence decreased (8.3% to 6.5%)
Asia				
Li et al, 2007 (Beijing, China) ⁸⁷	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1986–89; n=1090), wave 2 (1997–99; n=1593)	Prevalence and incidence of dementia (ICD–10, DSM–IV)	Prevalence increased (1.7% to 2.5%); incidence increased (0.6% to 0.9%)
Yu et al, 2012 (Hong Kong, China) ⁸⁸	Review	Age ≥70 years (1995–2006)	Prevalence of dementia (ICD–9, ICD–10)	Prevalence increased from 4.5% to 9.3%
Chan et al, 2013 (China) ⁸⁹	Systematic review of 75 cross-sectional surveys	Age ≥55 years (1990–2010; n=340 247)	Prevalence of dementia and AD (DSM–III, DSM–III–R, DSM–IV, NINCDS–ADRDA, ICD–9, ICD–10)	Prevalence increased in all age groups
Wu et al, 2014 (China, including Hong Kong and Taiwan) ⁹⁰	Systematic review of 70 prevalence studies	Age ≥60 years (1990–2012)	Prevalence of dementia by survey years, age groups, and birth cohorts (DSM–III, DSM–III–R, DSM–IV, ICD–10, others)	Controlling for methodological factors, prevalence increased slightly from 1995 to 2012; a birth cohort effect was reported (ie, a more recent cohort of the same age had higher dementia prevalence)
Sekita et al, 2010 (Hisayama, Japan) ⁹¹	Repeated cross-sectional surveys	Age ≥65 years for all waves: wave 1 (1985; n=887), wave 2 (1992; n=1189), wave 3 (1998; n=1437), wave 4 (2005; n=1566)	Prevalence of all-cause dementia and AD (DSM–III, DSM–III–R)	Prevalence increased from 1985 to 2005 for all-cause dementia (6.0% to 8.3%) and for AD (1.1% to 3.8%)
Dodge et al, 2012 (Japan) ⁹²	Systematic review of eight cross-sectional surveys	Age ≥65 years (1985–2008; n=13 396)	Prevalence of dementia (DSM–III, DSM–III–R, DSM–IV)	Prevalence increased (6.7% to 11.3%)
Population-based surveys and systematic reviews of population surveys about the temporal trends of dementia occurrence. AD=Alzheimer's disease. ICD=International Classification of Diseases criteria. NINCDS–ADRDA=National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. OR=odds ratio. DSM=Diagnostic and Statistical Manual of Mental Disorders criteria. NINDS–AIREN=National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria. IRR=incidence rate ratio.				
Table 3: Temporal trends of dementia occurrence according to continent				

risk of stroke and heart disease have had a substantial role in reducing the risk of dementia and AD, possibly by reducing the number of brain lesions and thereby

preventing or delaying the onset of dementia in the general population.^{86,103} In support of this notion, the Rotterdam Study has provided evidence that the suggested decline in

For more on the **Rotterdam Study** see <http://www.epib.nl/research/ergo.htm>

dementia incidence with time might be a result of less brain atrophy and less cerebral small vessel disease.⁸⁴

New evidence about temporal changes in dementia occurrence will affect estimates of worldwide and regional future burden of disease, because earlier estimates and projections were based on the assumption that age-specific prevalence of dementia remained constant. Even for regions such as Europe, with some evidence of declining prevalence or incidence, the future burden of dementia is likely to increase as a result of population ageing.

Dementia is not an unavoidable consequence of ageing

Genetic susceptibility, environmental factors (eg, psychosocial, lifestyle, and biological factors), and their interaction over the lifespan contribute to the pathological processes and clinical expression of dementia. However, not all nonagenarians, or even centenarians, develop AD or other dementias,^{104,105} which shows that some people are able to reach very advanced ages without severe mental deterioration. Neuropathologically, the population-based 90+ Autopsy Study, an ancillary of the 90+ Study of people aged 90 years or older in the USA, showed that nearly 50% of people with dementia did not have sufficient neuropathology in their brain to explain their cognitive symptoms.¹⁰⁶ By contrast, intermediate or high levels of AD pathology were present in about a third of very old people without dementia or cognitive impairment.¹⁰⁷ Furthermore, the association between the pathological hallmarks of AD—neuritic plaques (deposits of amyloid β peptide [A β]) and neurofibrillary tangles (aggregates of hyperphosphorylated tau protein)—and the clinical syndrome of dementia was less strong in the oldest old than in younger old people.^{108,109}

These findings indicate that certain compensatory factors—eg, high education, social engagement, maintenance of cardiovascular health—provide brain reserve (related to brain size, number of neuronal cells, or density of connections) and cognitive reserve (related to the brain's ability to use brain networks more efficiently or to recruit alternative networks in the presence of pathology),²⁷ which might enable individuals to tolerate a substantial amount of AD pathology without experiencing an obvious dementia syndrome, even in carriers of susceptibility genes for AD, such as the apolipoprotein E (APOE) $\epsilon 4$ allele.¹¹⁰ Several risk and protective factors are the focus of epidemiological studies and are discussed in more detail in the following subsections.

Risk and protective factors

Dementia, including AD, is a multifactorial disorder that is determined by the interplay of genetic susceptibility and environmental factors across the lifespan (panel 4). Older age is the strongest risk factor for AD and other dementias, and patients who develop dementia before age 65 years as a result of gene mutations (section 4) account for only a very small

proportion of all cases (1–5%). Most cases of dementia and AD are at least partly attributable to cardiovascular risk factors (eg, hypertension, diabetes, and obesity) and psychosocial factors (eg, education, social engagements, and leisure activities), which are the main modifiable factors that can be targeted for intervention (section 3). The qualitative and quantitative effects of most of these factors on AD and dementia have been assessed in several systematic reviews and meta-analyses.^{111,112}

Lifestyle-related cardiovascular risk factors

Smoking is associated with a 50–80% increased risk of dementia, and even second-hand smoking could increase dementia risk.^{113,114} Diabetes in middle age or later in life increases the risk not only of vascular dementia, but also of AD (by about 50%).^{115,116} By contrast, light-to-moderate alcohol consumption has been associated with a 30–40% reduced risk of dementia.^{117,118} Likewise, regular physical activity, even low-intensity activity such as walking, seems to reduce dementia risk by about 40%.¹¹⁹ Of note, systematic reviews from the life-course perspective (ie, from the point of view of exposure across the lifespan) have revealed age-dependent associations of dementia and AD with major cardiometabolic risk factors—including hypertension, high cholesterol, and obesity or overweight—such that having these factors in young adulthood or middle age (eg, age <65 years), but not necessarily in late life (eg, age ≥ 75 years), is associated with an increased risk of dementia and AD.^{112,120} Indeed, long-term follow-up studies^{121–124} reveal that blood pressure, total cholesterol, and body-mass index begin to decline years to decades before dementia onset, possibly as a result of ongoing AD pathology. Thus, low levels of these metabolic factors in later life might actually be part of prodromal (or preclinical) dementia.

More importantly, population-based studies have also shown that having multiple cardiovascular risk factors (eg, smoking, hypertension, diabetes, hypercholesterolaemia) concurrently in middle age or several years before dementia onset incrementally increases the risk of dementia and AD.¹²⁰ Thus, to delay the onset of dementia, the optimum time window for interventions that target lifestyle-related cardiovascular risk factors might be young adulthood or middle age, and interventions that target multiple domains are likely to be more effective. Indices for use in middle age or later life to predict dementia risk have been developed and validated, and have an accuracy of between 70% and 80%; unhealthy lifestyle and cardiometabolic risk factors constitute a major part of these indices.^{125–129}

Psychosocial factors

High educational achievement in early life has consistently been associated with reduced risk of late-life dementia and AD.¹³⁰ Cognitive activity or mentally stimulating activity (eg, reading, doing crossword puzzles, playing games), which might be related to early life education, has also

For more on the 90+ Study see
<http://90study.org/>

Panel 4: Putative risk and protective factors for late-onset dementia and Alzheimer's disease**Risk factors**

Older age

Genetic factors

- Familial aggregation (two or more family members with the disease)
- APOE ϵ 4 allele
- Other susceptibility genes (eg, CR1, PICALM, CLU, TREM2, TOMM40)

Vascular risk and metabolic factors

- Atherosclerosis
- Cerebral macrovascular and microvascular lesions
- Cardiovascular diseases
- Diabetes mellitus and pre-diabetes
- Midlife hypertension
- Midlife overweight and obesity
- Midlife high serum cholesterol

Lifestyle factors

- Sedentary lifestyle
- Smoking
- Heavy alcohol consumption

Diet and nutritional factors

- Saturated fats
- Hyperhomocysteinaemia
- Deficiencies in vitamin B6, B12, and folate

Other factors

- Depression
- Traumatic brain injury
- Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
- Infectious agents (eg, herpes simplex virus type 1, *Chlamydia pneumoniae*, spirochetes)

Protective factors

Genetic factors

- Some genes proposed (eg, APP, APOE ϵ 2 allele)

Psychosocial factors

- High education and socioeconomic status
- High work complexity
- Rich social network and social engagement
- Mentally stimulating activity

Lifestyle factors

- Physical activity
- Light-to-moderate alcohol intake

Diet and nutritional factors

- Mediterranean diet
- Polyunsaturated fatty acid and fish-related fats
- Vitamin B6, vitamin B12, and folate
- Antioxidant vitamins (A, C, E)
- Vitamin D

Drugs

- Antihypertensive drugs
- Statins
- Hormone replacement therapy
- Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer's disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two APOE ϵ 4 alleles.

APOE=apolipoprotein E. CR1=complement component receptor 1.

PICALM=phosphatidylinositol-binding clathrin assembly protein. CLU=clusterin.

TREM2=triggering receptor expressed on myeloid cells 2. TOMM40=translocase of outer mitochondrial membrane 40 homologue. APP=amyloid precursor protein.

been associated with reduced dementia risk, as have social engagement and maintenance of a rich social network. Finally, although the temporal relation between depression and dementia in older people remains debatable, evidence from long-term follow-up studies suggests that depression might be a risk factor for dementia and AD.^{131,132}

Potential pathological mechanisms

In the past decade, population-based neuroimaging and neuropathological studies have contributed substantially to understanding of the pathophysiological mechanisms linking cardiovascular risk factors and psychosocial factors to AD and dementia. Evidence from multi-disciplinary research points to vascular mechanisms and the importance of brain and cognitive reserve. Thus, two pathways could be targeted to prevent or delay the onset of dementia.

Vascular mechanisms

It is well known that cardiovascular risk factors (eg, hypertension and diabetes) cause cerebrovascular lesions.

Research has also provided evidence that these factors contribute to global and regional brain atrophic lesions (loss of brain tissue) and to neurodegenerative pathologies such as AD.^{133–135} Biologically, cerebral atherosclerosis and neurodegeneration might have shared mechanisms, such as oxidative stress (damage resulting from high levels of reactive oxygen species), inflammation, and deposition of toxic A β . Intracranial atherosclerosis could also induce cerebral hypoperfusion and trigger accelerated deposition of A β , which in turn contributes to cognitive deterioration and dementia.¹³⁶ Furthermore, cerebral macrovascular (eg, atherosclerosis and infarction), microvascular (eg, lacunar infarcts, white matter lesions, microbleeds), and neurodegenerative pathologies might converge during ageing to cause additive brain damage and thus promote clinical manifestation of a dementia syndrome.^{137–140} This possibility is supported by neuroimaging and neuropathological studies,^{141–143} which show that most cases of clinically diagnosed dementia and AD in older people living in the community are associated with mixed vascular and neurodegenerative pathologies in the brain.

Reserve hypothesis

Neuropathological studies have shown that psychosocial factors can modify the association of neurodegenerative pathologies with cognitive function, such that cognitive ability can remain high in individuals with a heavy burden of global neuropathology if they also engage in cognitively stimulating activities or have high levels of education or rich social networks.^{144–146} How these factors compensate for the deleterious effects of cerebrovascular and AD pathologies on cognitive performance in ageing remains open to debate. The related concepts of brain reserve and cognitive reserve are the focus of intensive research.²⁷

Public health implications

According to a US National Institutes of Health (NIH) state-of-the-science review¹⁴⁷ published in 2010, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or AD. Indeed, many studies have been hampered by methodological issues, such as self-reported measurements of exposure to risk factors, inconsistent control of relevant confounders (eg, depression), and variations in diagnostic procedure and criteria for dementia and AD.^{148,149} However, a different picture would have emerged if the evidence had been assessed from a life-course perspective.¹¹² For instance, a systematic review¹¹¹ of epidemiological studies that focused on seven modifiable risk factors (low education, smoking, diabetes, midlife hypertension, midlife obesity, depression, and physical inactivity) suggested that a 10% reduction in exposure to these risk factors in midlife could potentially prevent up to 1·1 million cases of AD per year worldwide. Therefore, the proper time windows over the lifespan (eg, midlife or younger old age) for intervention to prevent or delay the onset of dementia should be kept in mind when designing intervention programmes (section 3).¹⁵⁰

It has been suggested that some interventions (eg, pharmacological control of hypertension), if implemented in middle-aged or younger old adults, might effectively reduce the incidence of dementia.¹⁵¹ Thus, although age remains the main driving force for dementia development,¹⁵² interventions that target multiple modifiable risk factors, if implemented earlier in life, might be more promising than later interventions in reducing the risk or postponing the onset of dementia,⁷⁶ and several intervention studies to assess effects on disease onset are underway in Europe (section 3).¹⁵³ It has been estimated that delaying the onset of dementia by 5 years would halve the prevalence of dementia and substantially decrease the number of dementia cases in the community. Delaying the onset of dementia by even 2 years would have substantial public health, economic, and societal benefits.¹⁵⁴

Traumatic brain injury and dementia

Although a systematic review showed no convincing evidence in support of an increased risk of AD or dementia

after mild traumatic brain injury (TBI),¹⁵⁵ results of several epidemiological studies^{156–159} suggest that a history of head trauma or mild TBI is associated with an increased risk of AD and other dementias and results in an earlier age at onset in affected individuals compared with those without head trauma. Autopsy studies have shown substantial A β deposition in up to 30% of people who die acutely after a brain injury.^{160,161} Moreover, brain interstitial fluid concentrations of the aggregation-prone 42-aminoacid form of A β (A β 42) and the axonal injury marker tau are reported to be higher immediately after severe TBI.^{162–164}

A history of head trauma is associated with greater A β deposition in patients with mild cognitive impairment,¹⁶⁵ and data suggest that an important cause of dementia in individuals with a lifestyle associated with increased risk of repetitive mild TBI or concussion (the terms are used interchangeably) is chronic traumatic encephalopathy, a neuropathologically defined condition previously described in professional boxers.¹⁶⁶ It is now clear that athletes engaged in contact sports such as boxing, American football, and ice hockey constitute a new group at risk of dementia. The underlying mechanisms seem to involve diffuse axonal injury and A β and tau deposition resulting from repetitive acceleration–deceleration and rotational forces on the brain tissue.¹⁶⁶ Evidence of smaller hippocampus (a brain region associated with emotions, learning, and memory) volumes in American football players, of chronic traumatic encephalopathy pathology in American footballers, ice hockey players, and military personnel, and of biomarker changes associated with brain injury after sub-concussive head blows in amateur boxing emphasise the need to explore further the relation between TBI and dementia.^{167–169}

Summary and recommendations

Epidemiology has provided powerful methods to study the burden and geographical variations in the occurrence of AD and other dementias in society, to understand the natural history of dementia and identify risk and protective factors, to identify populations at increased risk of dementia, to monitor time trends in dementia occurrence, to investigate the effects of new therapies for dementia, and to assess the different protective strategies for intervention against dementia. However, we are still far from developing a cure or an effective pharmacotherapy for AD, providing cost-effective medical and social care for the many patients affected by dementia, and implementing successful intervention strategies against dementia.

Additional epidemiological surveillance is required to provide a complete picture of the epidemiology of dementia in Europe and worldwide. AD, which accounts for up to 70% of all dementia cases in most studies, is an age-related disease that develops over many years, but it is not an inevitable consequence of ageing—up to 50% of people who reach the age of 90 years do not have dementia—and more work is needed to understand why. From an epidemiological perspective, implementation of the

following recommendations will be key to meeting the future challenges of dementia and AD.

(1) A harmonised international database for population-based longitudinal studies of ageing and dementia should be established. The aim should be to provide powerful resources to further understand the burden (economic and societal costs), temporal trends (prevalence, incidence, and mortality), natural history (eg, with identification of genetic and clinical markers for early detection), and aetiopathogenesis (eg, exploration of the potential contributions of psychosocial stress, mild TBI, nutrition, and frailty) of AD and other dementias.^{99,170}

(2) Knowledge about the effects of dementia at the individual and societal levels is needed—such as prevalence stratified by severity, factors linked to progression in cognitive and functional disability, and factors linked to admission to institutions.

(3) Multidisciplinary research projects that integrate epidemiological approaches with genetic, neurobiological, neuroimaging, and clinicopathological techniques are needed to improve understanding of the pathophysiological processes of ageing and dementia. Such knowledge will facilitate the development of new therapeutic approaches for dementia in the clinical setting and intervention strategies against dementia in the community.

(4) Life-course approaches should be applied to epidemiological studies of AD and other dementias. These approaches are particularly relevant with regard to understanding the causes and natural history of dementia, and in developing intervention strategies for multifactorial chronic diseases such as AD.

(5) Long-term studies with harmonised methods should be done to understand better the temporal trends and geographical variations of dementia occurrence within single countries and across Europe. In particular, more research is needed to clarify whether and to what extent the secular trends in cardiovascular risk and dementia occurrence in Europe are causatively correlated.

(6) A collaborative project in Europe should be initiated to understand the occurrence, non-genetic determinants, natural history, and individual and societal burden of early-onset dementia.^{171,172}

Section 3. Prevention of cognitive impairment and dementia

WHO³ and health and science ministers of the G8 dementia summit¹⁷³ have recognised dementia as a public health priority, and prevention has been identified as one of the key elements in addressing the dementia epidemic, as for other major non-communicable diseases (eg, cardiovascular disease). It is estimated that a third of AD cases worldwide might be attributable to seven modifiable risk factors—low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression—and a reduction in the prevalence of these risk factors by 10–20% per

decade could reduce the worldwide prevalence of AD in 2050 by 8–15% (between 8·8–16·2 million cases).¹⁷⁴ Furthermore, delaying the onset of dementia by just 5 years might reduce the number of cases in total by up to 50% over 50 years.^{175,176}

Observational studies in the general population, starting in early adulthood, are needed to monitor the distribution of risk and protective factors in different age groups and in different generations over long periods. Few such studies have been done, and data from the 1960s and 1970s might not be entirely applicable because of changes in lifestyle, society, pharmacological treatments, and the type of risk factors.¹⁷⁷ In the past few decades, for example, there has been a widespread and substantial increase in the prevalence of obesity and diabetes mellitus.^{178,179} Knowledge about risk-factor distribution in different populations can help to obtain reliable estimates of the effects of preventive interventions on future dementia prevalence, thus aiding health education and community planning.

Epidemiological studies can identify potential modifiable risk and protective factors that could be targeted in dementia prevention programmes (section 2). However, a big challenge is to design such programmes on the basis of firm evidence from well designed and ethically sound clinical studies. Large-scale randomised controlled trials (RCTs) are needed to establish whether prevention strategies that target potential risk and protective factors—from lifestyle factors to drugs for prevention, including multifactorial interventions—can decrease substantially the incidence of dementia.

Evidence from observational studies and clinical trials

During the past 10–15 years, various modifiable risk and protective factors have been linked in long-term observational studies to an increased risk of dementia and AD (panel 4). Vascular risk factors at midlife (eg, high blood pressure, cholesterol, obesity, diabetes) have been linked to an increased risk of dementia and AD later in life.⁷⁶ Psychosocial factors, such as depression, loneliness, and stress, have also been identified as possible risk factors.^{76,177} Conversely, factors such as physical, cognitive, and social activities and healthy diet might reduce the risk of dementia.^{76,177} Complex gene–environment interactions underlie the development of dementia, and some environmental factors might have more pronounced effects in genetically susceptible individuals, such as carriers of the *APOE* ε4 allele, the most important genetic risk factor for sporadic AD (section 4).^{76,177}

Although observational studies have provided information about potential modifiable risk and protective factors, large RCTs are needed to confirm that interventions targeting these factors can efficiently postpone or prevent cognitive impairment and dementia, and to test which of a wide range of interventions are most effective in preventing or delaying onset in different

at-risk groups. Positive results from observational studies have not automatically led to successful prevention strategies in RCTs. For example, encouraging data from observational studies of the preventive properties of hormone replacement therapy (HRT) and non-steroidal anti-inflammatory drugs (NSAIDs) were not confirmed in RCTs.^{180–182} An important reason for this disparity is the problematic translation of observational data into intervention design. Trials based on the assumption that AD is a monodimensional condition (ie, due mainly to a single risk factor or cause) have consistently failed to identify efficacious prevention interventions. Additionally, use of compounds with different mechanisms of action (eg, HRT, NSAIDs, statins, vitamins, ginkgo biloba extract) has often been tested in prevention RCTs that were add-ons to trials with other primary outcomes (eg, cardiovascular or cerebrovascular events).¹⁷⁷ Such trial designs might have limited the ability to detect an effect on cognition or dementia risk because of low statistical power or short duration. So far, no study has convincingly shown a single-drug approach to be effective in the prevention of dementia. Antihypertensive drugs are the only exception, with some evidence for a protective effect against dementia.¹⁸³ Single lifestyle-related intervention trials (eg, physical activity and cognitive training) have shown only modest or short-term positive results.¹⁴⁷

Prevention RCTs have highlighted several key issues that should be taken into account when designing and testing prevention strategies.¹⁸⁴ Effective approaches depend on appropriate timing of the intervention. Starting during preclinical or prodromal AD—ie, before the onset of dementia—is likely to be more effective than starting when dementia is already established, and some interventions might have critical time windows (eg, beneficial effects only in midlife or during the preclinical phase). Preventive measures need to be adjusted to their intended target groups, and larger trials (ie, several thousand participants instead of hundreds) with longer-term interventions (ie, years instead of months) are needed to show preventive effects in healthy, younger individuals (around 60 years of age). The very definition of “effects” is important, and measuring changes in performance with cognitive tests that can capture subtle decline and the entire continuum of cognitive functioning might be a more sensitive outcome than conversion to dementia. In multifactorial disorders, single-agent interventions might not be enough to significantly affect cognition and function, and targeting several risk factors and disease mechanisms simultaneously might be needed for optimum preventive effects.

Some risk or protective factors for dementia and AD have been investigated in clinical trials, but the amount and quality of available evidence for such factors is variable. Moreover, opinions are divided about what constitutes sufficient evidence to formulate specific prevention recommendations. RCTs are usually thought

to provide the best evidence that an intervention has clinically meaningful effects. However, traditional RCTs are not always possible. Vascular risk factors cannot be left untreated in placebo groups for ethical reasons (there is already strong evidence that treating vascular risk factors protects against cardiovascular disease), and strict double-blinding is not always possible with lifestyle-related interventions. Vascular risk factors in midlife have been linked to an increased risk of dementia and AD 20–30 years later in long-term population-based observational studies.⁷⁶ However, it is not feasible to do such long-term RCTs to verify these effects. It would also be counterproductive to wait for successful RCTs before implementing every prevention strategy. The relation between smoking and lung cancer is a classic example of observational studies providing sufficient evidence for prevention. No RCTs have been needed for non-smoking guidelines and recommendations, because these studies would have been unethical.

As mentioned in section 2, epidemiological studies in several high-income countries (eg, the USA, the Netherlands, Sweden, the UK) suggest that the incidence or age-specific prevalence of dementia has declined in the past 20 years.^{68,84,86} These findings imply that dementia risk is modifiable. Possible explanations for the fall in incidence include favourable changes in some vascular risk factors (eg, better and wider use of drugs and changes in behaviour), changes in education or employment, and fewer head injuries.

Research in progress

Several countries have already taken the step from observation to action and initiated large lifestyle-based multifactorial intervention trials. This approach includes interventions that target several risk factors simultaneously in individuals who are at increased risk of dementia. Table 4 summarises the main trials completed or in progress in Europe.^{185–188} An at-risk group was selected for the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study (ClinicalTrials.gov identifier NCT01041989) according to the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score, the first tool for estimating long-term risk of dementia on the basis of risk factors present at midlife (table 5). The CAIDE risk score, which has been validated in a large multi-ethnic population in the USA,¹²⁸ can help to identify individuals who might benefit from intensive lifestyle consultations and pharmacological interventions (ie, target interventions for those most at risk). The risk score can also be used as an educational and motivational tool—eg, to distribute easily understandable information about risk factors to those most at risk in the general population.

In the FINGER RCT, the 2 year multidomain intervention consisted of four components: nutritional guidance, physical exercise, cognitive training and social activity, and management of vascular risk factors. The

For more on the FINGER project
see <https://www.thl.fi/fi/web/thlfi-en/research-and-expertwork/projects-and-programmes/finger-research-project>

first results from this study suggest that it is possible to improve lifestyle factors in older adults at risk of dementia, and that such changes can significantly enhance cognitive performance and reduce the risk of cognitive decline.¹⁸⁹ Extended follow-up of FINGER study participants is ongoing to detect differences in dementia and AD incidence.

Another new approach is the use of technology. For example, in the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) project (ISRCTN registry identifier ISRCTN48151589), an internet-based platform has been developed that aims to motivate and support lifestyle changes and improve management of cardiovascular factors. The platform is interactive, with nurse or coach support readily available, and the project will test whether making prevention more accessible for elderly people in the community can reduce cardiovascular risk factors and dementia. Finally, as part of the European Dementia Prevention Initiative (EDPI), a data-sharing platform has been established between the multidomain prevention RCTs in progress in Europe to allow in-depth joint analyses of data relating to different target groups and interventions, and collaborations between research groups in different countries. Differences in health-care systems across Europe can be taken into account in such analyses, which will be crucial in the planning of future multinational prevention studies and programmes.

Increased collaboration between governments and between research groups, including public and private institutions, is necessary to create the infrastructure needed for research into prevention of dementia and AD, and to facilitate the implementation of evidence-based prevention strategies. Some international large-scale initiatives have already been established to increase collaboration, including the EU Joint Programme for Neurodegenerative Disease Research (JPND), the Innovative Medicines Initiative, the G8 dementia summit,¹⁷³ and the Organisation for Economic Co-operation and Development's (OECD) mapping for big data in Alzheimer's research.¹⁹⁰ A common aim of these initiatives is to increase and coordinate investments and collaborations between participating countries by bringing together academic experts, private sectors (the pharmaceutical and other industries), and policy makers and by building on existing infrastructures. The main goal is to investigate key research questions about neurodegenerative diseases, including AD, and identify effective preventive and therapeutic measures that can be implemented in different settings (eg, in the general population and in clinical settings).

For more on the **JPND research initiative** see <http://www.neurodegenerationresearch.eu/>

For more on the **Innovative Medicines Initiative** see <http://www.imi.europa.eu/>

For more on the **HATICE project** see <http://www.hatice.eu/>

For more on the **EDPI collaboration** see <http://www.edpi.org/>

Prevention trials in populations at high risk of dementia

Increasing evidence that the disease process (ie, accumulation of pathology) can start many years before

	FINGER¹⁸⁵	MAPT¹⁸⁶	PreDIVA¹⁸⁷	HATICE¹⁸⁸
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1.5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

Table 4: Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease

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	Points
Age	
<47 years	0
47–53 years	3
>53 years	4
Education	
>9 years	0
7–9 years	2
<7 years	3
Sex	
Female	0
Male	1
Blood pressure	
≤140 mm Hg	0
>140 mm Hg	2
Body-mass index	
≤30 kg/m ²	0
>30 kg/m ²	2
Total cholesterol	
≤6.5 mmol/L	0
>6.5 mmol/L	2
Physical activity	
Yes	0
No	1

Probability of developing dementia in 20 years according to CAIDE midlife risk score categories. A total score of 0–5 corresponds to a dementia risk of 1.0%, a score of 6–7 to a risk of 1.9%, a score of 8–9 to a risk of 4.2%, a score of 10–11 to a risk of 7.4%, and a score of 12–15 to a risk of 16.4%. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia.

Table 5: CAIDE risk score

For more on the **A4 study** see
<http://a4study.org/>

the onset of cognitive impairment and dementia in people with AD has driven a shift in focus from advanced disease to earlier stages, with trials for prevention (delaying or preventing disease onset) and treatment (targeting disease mechanisms to modify disease course) now targeting very similar groups of people in the preclinical stages of AD. Potential disease-modifying treatments (eg, anti-amyloid drugs), which were previously tested only in patients with AD dementia with a view to stopping or slowing the course of the disease, are now being tested in selected asymptomatic populations who are at high risk of AD because of an established biomarker burden or a specific genetic profile (section 7).¹⁹¹ For example, the safety and efficacy of anti-amyloid drugs as preventives in participants with pre-symptomatic (or preclinical) AD are being tested in three RCTs, two of which focus on early-onset familial AD and one on sporadic AD.

The Dominantly Inherited Alzheimer Network (DIAN; NCT01760005) and the Alzheimer's Prevention Initiative (API; NCT01998841) studies have enrolled individuals who carry mutations in one of *APP*, *PSEN1*, or *PSEN2*. These mutations cause dominantly inherited, early-onset AD, in which just one copy of the mutated gene in each

cell is sufficient to cause the disease (autosomal dominant AD). Although such cases of early-onset familial disease account for only 1–5% of all cases, the fact that progression to symptomatic AD is almost inevitable in this group makes their inclusion in prevention and treatment trials an important endeavour.

Data from the DIAN study, an international study with 210 participants from North America, Australia, and Europe, have shown that phenotypic changes associated with the disease can be detected several years before the onset of cognitive symptoms in people with autosomal dominant AD—cerebrospinal fluid (CSF) concentrations of Aβ42 decline 25 years before expected symptom onset, and brain deposition of Aβ can be detected 15 years before symptoms emerge¹⁹²—and the aim is to intervene before symptoms emerge in this high-risk group. The API trial focuses on the world's largest early-onset AD kindred, in Antioquia, Colombia. Of about 5000 individuals in this kindred, around 1500 carry a mutation in *PSEN1* (E280A), which causes disease with a mean age of onset of 45 years.¹⁹³ The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study (NCT02008357) aims to prevent sporadic AD and assess the effect of an anti-amyloid compound in older adults with evidence of brain amyloid accumulation at neuroimaging assessment. The A4 study includes an ethics arm, which is examining the psychological effects of disclosing information to individuals about their risk of developing AD.¹⁹⁴

Although Europe has been at the forefront of initiatives to promote lifestyle-based interventions for dementia prevention, North America has led the start of RCTs of anti-AD drugs in preclinical AD. However, studies of both pharmacological and non-pharmacological interventions for the prevention of cognitive decline and dementia are now being started in several world regions. In Europe, the launch of the European Prevention of Alzheimer's Dementia Consortium (EPAD), within the Innovative Medicines Initiative, is expected to create readiness cohorts and a novel framework for RCT testing of new disease-modifying drugs in the preclinical stages of AD. Indeed, enough evidence exists to justify some immediate actions in dementia prevention,¹⁹⁵ including public health policies that encourage middle-aged people to stop smoking, treat high blood pressure, and avoid obesity and diabetes.

Health economics of dementia prevention

Assessing the benefits of delaying or preventing the onset of dementia from an economic perspective is a complex endeavour. AD has a long, silent phase before the first symptoms emerge, and it can take time for milder symptoms to develop into full-blown dementia. Healthcare services are needed less and costs are lower in the early stages of cognitive impairment than in the later stages of disease (section 1). Among the challenges of assessing the benefits of preventive strategies is

For more on the **EPAD project**
 see <http://www.ep-ad.org>

For more on the **DIAN study** see
<http://www.dian-info.org/>

For more on the **API study** see
<http://banneralz.org/research-plus-discovery/alzheimers-prevention-initiative.aspx>

intervention methodology. For example, because dementia incidence is strongly related to age and dementia is rare in midlife, a very broad intervention in younger individuals (around 40–50 years) with no symptoms will be associated with a very low occurrence of dementia. Some prevention activities, such as targeting vascular and lifestyle factors, are implicit in daily life and in medical-care settings, making it difficult to estimate their costs separately. Public health prevention trials outside the medical-care system are easier to assess than trials embedded in the system, because the former tend to demand some kind of separate infrastructure, with associated programme costs.

Approaches such as economic simulations can be useful for the estimation of cost-effectiveness. For example, one study¹⁹⁶ assessed the cost-effectiveness of a potential dementia prevention programme using the CAIDE risk score and a Markov model adapted to Swedish conditions. The prevention programme consisted of a healthy-lifestyle promotion programme and pharmacological treatment of cardiovascular risk factors. Figures for costs (intervention costs and costs of care for people with and without dementia), utilities (health utilities expressed as QALYs), and mortality according to age group were obtained from published work or databases. The multidomain preventive intervention was less costly and was associated with better dementia-related outcomes than was usual care, supporting its cost-effectiveness. Thus, to assess the cost-effectiveness of prevention programmes, a multifactorial approach is desirable, with a filter to select at-risk participants and sufficient statistical power in terms of sample size and intervention duration.

Summary and recommendations

The pathology of AD is complex, but epidemiological studies have provided knowledge of protective factors and risk factors for the disease. The onset of AD and other dementias could probably be prevented or delayed, because many of the known risk factors are modifiable or amenable to management. Enough evidence exists to justify some immediate actions in dementia prevention,¹⁹⁵ including public health policies that encourage middle-aged people to stop smoking, treat high blood pressure, avoid obesity and diabetes, and increase their physical activity. However, knowledge about modifiable risk factors needs to be refined, and findings from observational studies need to be validated in large, well designed, and ethically sound intervention studies. Here we identify priorities for the implementation of effective dementia prevention programmes.

(1) Many modifiable risk factors—including high blood pressure, obesity, physical inactivity, and unhealthy diet—are shared among dementias, including AD, and other major late-life chronic disorders, such as heart disease and stroke. Public health efforts should aim to promote healthier lifestyles in midlife, because this approach has the potential to improve the general health status of the population in advanced age.

(2) Population surveillance of risk factors in different age groups and different countries is urgently needed to better estimate the effects of preventive interventions on future dementia and AD prevalence across Europe. This information should be used in the planning of public health policy.

(3) Observational studies need to start early in midlife and have a long duration to identify windows of opportunity for effective interventions. By building on existing infrastructures and cohorts developed for the study of other chronic diseases, resource use could be optimised.

(4) Effective prevention of dementia demands tailored intervention strategies for particular target groups (eg, appropriate interventions for different ages and contexts). The characteristics of target groups, in addition to differences in health-care systems between countries, need to be considered in developing preventive strategies that can be translated easily and implemented internationally.

(5) In view of the multifactorial causes of AD and dementia, multidomain interventions—with simultaneous management of various risk and protective factors through lifestyle changes and pharmacological treatment—should be considered for optimum preventive effects.

(6) Increased collaboration between governments and between public and private institutions will help to accelerate and increase the power of prevention research for AD and dementia. To allow scientific collaboration between research groups in Europe, an appropriate infrastructure is needed to enable more effective use of existing data and rapid recruitment of participants in multinational intervention trials.

Section 4. Genetic risk of Alzheimer's disease: individual susceptibility

Evidence from genetic studies explains how genetic variability, present in DNA from conception, contributes to the development of AD later in life. Genetic epidemiology attempts to understand how genetic make-up lends resistance or vulnerability to environmental exposures, such as lifestyle factors and medical illnesses. The effect of individual genetic susceptibility on the occurrence of AD is substantial, with the heritability of AD usually estimated to be greater than 60% (ie, >60% of variation in the phenotype is genetically determined).¹⁹⁷ Specialist terms that are key to our discussion in this section are defined in panel 3.

Several specific gene mutations cause, or contribute to, early-onset familial AD. About 5% of all patients have early-onset AD (age at onset younger than 65 years), and up to 2%—ie, about half of early-onset cases—will have autosomal dominant inheritance in the family, in which the occurrence of the disease is explained by mutations in one gene with a major effect. A mutation in *APP*, which was shown in 1991 to be associated with a familial form of early-onset AD,¹⁹⁸ was the first known genetic determinant of the disease. Since then, mutations in the

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APP, *PSEN1*,¹⁹⁹ and *PSEN2*²⁰⁰ genes have been shown to account for almost half of all cases of early-onset familial AD. Most of these monogenic hereditary forms of AD follow a mendelian autosomal dominant transmission, affecting at least one individual in each generation.

For the other 98% of AD cases—sporadic AD, with late onset in most patients—clinicians often identify a family history of dementia without any specific mode of transmission, although the precise estimation of family history can be difficult because diagnostic assessments were limited in the past and the patient's parents might no longer be alive. The first susceptibility gene in sporadic AD, the $\epsilon 4$ allele of *APOE*, was discovered in 1993.^{201,202} By contrast with *APP* mutations, polymorphism of the *APOE* $\epsilon 4$ allele is frequent in the general population, with a codominant effect on AD risk. The odds ratio (OR) is estimated to be 3.2 and 14.9 for carriers of one or two $\epsilon 4$ alleles, respectively (ie, the odds of having AD is about three times higher in people with one *APOE* $\epsilon 4$ allele than in people without the allele), with a high attributable fraction in the population (between 20% and 40%).²⁰³ Many genetic variants that increase susceptibility to AD have since been identified (table 6).

Genetics plays a major part in understanding the disease mechanisms of AD, and will have an important role in prevention and care in the future. For example, genetic tests can be used to identify and classify individuals with various levels of risk for AD, ranging from low to high, before symptoms have appeared (predictive pre-symptomatic genetic testing), and for early diagnosis in prodromal states of AD. A detailed understanding of the level of AD incidence associated

with genetic susceptibility will be important once an effective treatment is available, because genetic testing could then be used to identify and treat at-risk individuals before symptoms of cognitive dysfunction have developed. Genetic discoveries also offer clues to the pathological processes involved in the development of AD, and potential treatment approaches can be developed to intervene in these processes.

Progress of genomics: international collaboration and data sharing

Between 1995 and 2009, more than 500 potential new susceptibility genes were reported, but none of them could be consistently replicated and confirmed.²⁰⁴ The first achievement of the Human Genome Project²⁰⁵ and the incredible development of nano-genome-sequencing technologies in the biological sciences²⁰⁶ were needed to start to decipher the genetic susceptibility to AD.

The genome-wide association study (GWAS) approach that was developed thanks to these new technical developments has enabled the identification of a large proportion of genetic susceptibility to human diseases. Based on high-throughput genomics technologies, the GWAS approach can characterise millions of single-nucleotide polymorphisms (SNPs) covering the entire genome of one individual and offer a comprehensive view of the genomic regions associated with diseases. However, testing millions of variables in a case-control study design can lead to the discovery of false-positive associations. Thus, AD geneticists had to use very stringent p-value thresholds ($<5 \times 10^{-8}$) and to replicate systematically their discoveries in additional follow-up studies.²⁰⁷ Consequently, they had to enlarge the size of their samples from hundreds to thousands of cases and controls to increase their statistical power, improving the chances of detecting frequent polymorphisms with small individual effects on disease risk. The only way to collect very large samples of cases and controls was to create large collaborative consortiums that could share their clinical data, biobanks, and genotypes.

In 2009, two such consortiums, the European Alzheimer's Disease Initiative (EADI) and the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) consortium, discovered three new AD susceptibility loci.^{208,209} In 2010, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), in collaboration with EADI and GERAD, published two new loci,²¹⁰ one of which was confirmed. In 2011, the Alzheimer's Disease Genetics Consortium (ADGC) published, back-to-back with a paper from the three other consortiums,²¹¹ five new loci.²¹² Thus, the total number of susceptibility loci associated with late-onset AD was ten, including *APOE*. These four consortiums have formed the largest and most efficient genomics collaboration in AD, the International Genomics of Alzheimer's Project (IGAP), which has a combined sample population of 25 580 AD cases and 48 466 controls, and has discovered

For more on the CHARGE consortium see <http://www.chargeconsortium.com/>

For more on the ADGC collection see <https://www.niagads.org/content/alzheimers-disease-genetics-consortium-adgc-collection>

For the IGAP summary results see http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php

	Very rare (MAF <0.1%) familial variants	Variants present at low frequency (MAF <1%) in the population	Variants present as common polymorphisms (MAF >10%) in the population
Disease gene	<i>APP</i> , <i>PSEN1</i> , <i>PSEN2</i>
High impact (OR ≥ 2)	<i>SORL1</i>	<i>PLD3</i> , <i>TREM2</i> <i>APP</i> A673T (protective)	<i>APOE</i> $\epsilon 4$ allele <i>APOE</i> $\epsilon 2$ allele (protective)
Low impact (OR <2)	Confirmed loci: <i>ABCA7</i> , <i>BIN1</i> , <i>CASS4</i> , <i>CD2AP</i> , <i>CD33</i> , <i>CELF1</i> , <i>CLU</i> , <i>CR1</i> , <i>EPHA1</i> , <i>FERMT2</i> , <i>HLA DRB5-DRB1</i> , <i>INPP5D</i> , <i>MEF2C</i> , <i>MS4A6A/MS4A4E</i> , <i>NME8</i> , <i>PICALM</i> , <i>PTK2B</i> , <i>SLC24A4</i> , <i>SORL1</i> , <i>ZCWPW1</i> Unconfirmed loci: <i>ACE</i> , <i>ADAMTS20</i> , <i>AP2A2</i> , <i>ECHDC3</i> , <i>FRMD4</i> , <i>HS3ST1</i> , <i>IGH</i> , <i>NDUFAF6</i> , rs6678275 (intergenic), <i>SCIMP</i> , <i>SPPL2A</i> , <i>SQSTM1</i> , <i>TREML2</i> , <i>TRIP4</i>

Identified genes and loci classified according to their effect on the risk for Alzheimer's disease. Generally, causal mutations (associated with early-onset familial disease) are rare and deterministic, which means that they contribute to only a minor fraction of the total number of patients with AD but have a strong impact on the individual (very strong association), being sufficient to cause the disease. These genes are thus classified separately as disease genes. MAF=minor allele frequency. OR=odds ratio.

Table 6: Identified loci with genetic association to Alzheimer's disease

and confirmed 11 new loci and proposed 13 potential new loci.²¹³ Finally, four other genes were identified with different approaches. In 2015, the total number of confirmed genetic effects was 26, with 14 that still need to be validated, located in 39 different loci (table 6; appendix). A substantial proportion of the associated loci have unknown function.

Effects and frequencies of genetic variants

AD-associated loci can be classified into different groups in terms of genetic influence depending on the level of association of the genetic variant with the disease risk (weak or strong) and the frequency of this genetic variant in the general population (table 6). Whereas causal mutations (those associated with early-onset familial AD) are rare and deterministic, contributing to only a minor fraction of cases in the population but having a strong effect on the individual (very strong association), susceptibility genetic variants are usually more common in the population (SNPs with a minor allele frequency [MAF] >10%), and thus an association can have a large effect on the total burden of disease in the population but a small effect on individual risk. Susceptibility loci can have a high impact (OR ≥2) or low impact (<2), depending on how strong the association is to AD.

Causal mutations (disease genes) have been identified in segregation studies of familial forms of AD in which disease inheritance supports the involvement of a single gene mutation as the cause of the disease. Most high-impact susceptibility loci have been identified through hypothesis-driven candidate-gene approaches, targeting one or a few specific genes on the basis of their biological function or systematic sequencing approaches associated with functional studies. Low-impact susceptibility loci have been identified by GWAS, which are based on the association of SNPs to a disease with no a-priori hypotheses. In the absence of any functional or experimental information about the identified loci, GWAS results refer in general to susceptibility loci, largely without any known functional implications in terms of disease aetiology.

Disease genes (causal mutations) and the high-impact susceptibility loci discovered in familial forms of AD form the first two groups of disease loci in table 6. Deterministic mutations in *APP*, *PSEN1*, and *PSEN2*—all of which are involved in Aβ production—in early-onset monogenic forms of AD contributed to the amyloid cascade hypothesis of the disease (section 5), which posits that the Aβ peptide is a key player in AD causation.²¹⁴ However, mutations in these three genes are present in only about half of the families with autosomal dominant AD, which suggests that other major genes are still to be discovered. Systematic sequencing of exomes (ie, protein-coding regions) in autosomal dominant early-onset familial forms of the disease led to the discovery of nonsense and missense mutations in *SORL1* that are not detected in large control samples. Following

in-silico analyses, the mutations in *SORL1*, which encodes the sortilin-related receptor LR11/SorLA, a protein involved in the control of Aβ peptide production, seem likely to have a pathogenetic effect.²¹⁵ This finding provides support for the amyloid cascade hypothesis in early-onset forms of AD. Common polymorphisms of *SORL1* are also associated with sporadic AD.

See Online for appendix

The first and only gene to be consistently associated with sporadic AD with an older age at onset was *APOE*, which constitutes the third group of disease loci, with high frequency in the population and a high impact on disease risk (table 6). *APOE* was already known to be associated with high concentrations of LDL cholesterol and myocardial infarction risk.^{216,217} The risk effect of the *APOE* ε4 allele in AD was discovered with candidate-gene approaches.^{201,202} More in-depth analyses showed that the *APOE* ε2 allele was, conversely, a protective factor that reduced the risk for AD.²¹⁸ In recent studies, lifetime risk for AD, without reference to the *APOE* genotype, at age 85 years was 11% in men and 14% in women. This lifetime risk was 50% for *APOE* ε4 homozygous men and 60% for homozygous women, whereas for heterozygous *APOE* ε3ε4 carriers the lifetime risks were 23% for men and 30% for women. These estimations are consistent with a semi-dominant inheritance of a moderately penetrant gene (penetrance is the proportion of people with the variant who develop the associated disease), similar to the effect of *BRCA1* mutations on risk for breast cancer and other major-effect genes with incomplete penetrance in mendelian diseases.²¹⁹ Despite this major susceptibility impact on AD, the role of *APOE* in pathophysiology is open to debate.

Since 2009, several international research consortiums have contributed to the identification of susceptibility loci with high frequency and low impact, the fourth group of loci associated with AD (table 6).^{208–213} The total number of confirmed loci is 20, with 14 loci to be determined. The SNPs identified in these loci are frequent (MAF >10%), and are either protective (the minor allele is more common in the control group than in those with AD, and therefore associated with a lower risk) or deleterious (the minor allele is more common in those with AD than in the control group, and is therefore associated with increased risk), but with low impact (OR <2). All the loci in this fourth group need to be investigated to understand through which biological disturbances the genetic variants contribute to the development of AD. Some of the associated loci point to a specific gene, whereas others cover larger regions with several possible candidates. Thus, future research must focus on the identification of the specific genetic variants that cause the increased risk of AD and subsequent functional studies should unravel their biological relevance in pathophysiology.²²⁰

With the development of next-generation sequencing technologies, the exomes of a given genome can now be sequenced to characterise all the mutations present in the coding regions of patients and to examine their

presence or absence in controls. This sequencing approach was successfully used to discover two new AD genes with low-frequency mutations (MAF <1%) and high impact (almost as high as that observed for heterozygous *APOE* $\epsilon 4$ allele carriers), which constitute a fifth group of susceptibility genes (table 6). The first gene was triggering receptor expressed on myeloid cells 2 (*TREM2*), which had previously been associated with Nasu-Hakola disease, a rare disorder in which patients present with bone cysts and early-onset dementia.²²¹ While sequencing *TREM2* in a series of AD cases and controls, several low-frequency mutations could be identified and were associated with an increased risk (by more than four times) of sporadic AD.²²² *TREM2* was simultaneously discovered in an Icelandic population and similarly extended to sporadic AD risk in other populations.²²³

The phospholipase D3 (*PLD3*) gene was recently added to this fifth group.²²⁴ A non-synonymous coding mutation was discovered in a whole-exome sequencing study of 14 large families with late-onset AD in four or more individuals. The *PLD3* mutation segregated with AD in two independent families and doubled the risk for AD in a large case-control multicentre study. However, this observation could not be replicated.²²⁵ Functional experiments suggested that *TREM2* is related to the immune pathway, which has previously been implicated in AD pathogenesis. Finally, while searching for rare variants in the *APP* gene with a clinically significant effect on AD risk, Icelandic researchers identified a coding mutation (A673T) that potentially protects against AD and cognitive decline in the elderly population.²²⁶

From gene discovery to clinical application

Early-onset and late-onset AD genes

More than 200 different mutations in *APP*, *PSEN1*, or *PSEN2* have been identified in cases of early-onset AD. These mutations are usually inherited from an affected parent in an autosomal dominant manner, which suggests that new (de-novo) mutations are rare and penetrance is generally high, reaching almost a 100% lifetime risk. There have also been two reports of recessive *APP* mutations in rare cases.^{227,228} Thus, by screening for mutations in *APP*, *PSEN1*, and *PSEN2* in individuals affected by AD who belong to families with dominant inheritance and early onset of disease, the causal mutation can be identified in almost 50% cases. This type of mutation screening in known genes could be applied in clinical practice as a genetic diagnostic test.

If a mutation is identified in an index case from a family with inherited AD, genetic testing can be used to predict the risk in relatives who are still asymptomatic, a procedure known as pre-symptomatic genetic testing. The ability to identify at-risk individuals very early, before the disease process starts and when few comorbidities are present, provides researchers with an important

opportunity to increase understanding of AD by tracing the natural history of the disease, the details of which will have implications for treatment and prevention. Several studies of early-onset AD show that the underlying pathophysiological process begins several years before definite clinical symptoms appear. Thus, studies of at-risk individuals from families with early-onset AD caused by mutations in *APP*, *PSEN1*, or *PSEN2* might shed light on the disease process in sporadic AD.²²⁹

Several research groups have studied the natural history of early-onset familial AD through prospective examinations of healthy, asymptomatic mutation carriers and their healthy non-carrier siblings. In these autosomal dominant AD cases, pathophysiological changes can be detected decades before any cognitive symptoms emerge.^{192,230–232} For example, concentrations of A β 42 in the CSF decline about 25 years before expected symptom onset, and A β deposition, as measured by positron emission tomography (PET), is detected 15 years before, as are increased CSF concentrations of tau protein and increased brain atrophy. Given the low frequencies of these familial forms of AD, the DIAN study was launched to examine the temporal progression of biomarker change using, for example, imaging, neuropsychological tests, and CSF analyses.²³³ Moreover, in a prospective study of healthy people older than 65 years who were followed up for more than 15 years, the first decline in cognitive performance (eg, measures of semantic memory) was noted 12 years before the diagnosis of AD.²³⁴ Improved understanding of the preclinical and clinical course of sporadic and familial AD could ultimately enable intervention before symptoms emerge.

In addition to *APOE*, the GWAS approach has identified several susceptibility loci whose relative contribution to the total load of AD in the population is high compared with the population attributable fraction of risk associated with the rare genes for early-onset AD (appendix). However, the use of this susceptibility information in any genetic testing at the individual level remains very limited because it does not provide reliable risk estimates.

Finally, other unknown genetic susceptibilities might result from interactions with environmental factors and other genes, and from mechanisms that are as yet unknown. These other potential mechanisms of action include epigenetic modifications of DNA and DNA-binding proteins, such as cysteine methylation and histone acetylation, and somatic mutations in the target tissue (ie, nerve cells).²³⁵ However, insufficient data exist for the relevance of these mechanisms in AD, and future research is needed to address such hypotheses. To decipher these complex genetic mechanisms, increased access to high-quality databases of detailed electronic health records and to biobanks is needed to correlate genotype to phenotype and to estimate interactions between contributing genetic and environmental factors.

Genetic testing

Much work remains to elucidate disease mechanisms in AD. However, the amount of data already accumulated from genetics and genomics prompts thinking about the relevance of this information for translational research and clinical practice. Three important applications in the medium term are risk prediction in research and clinical practice, clinical-trial enrichment (eg, screening for specific susceptibility genes to recruit a more homogeneous sample for drug testing), and precision medicine.

The most obvious application of genomics in clinical practice resides in the use of genetic testing to support early and pre-symptomatic diagnosis. However, the clinical value of preclinical genetic testing for sporadic AD in the absence of proven interventions that can stop or delay the disease process is questionable and raises ethical concerns. Thus, the major use of genomics in AD is to increase scientific knowledge about the disease and to improve translational and clinical research.

In families with a strong history of early-onset AD, clinical genetic testing might be requested by patients themselves. Such cases should be handled in a clinical genetics setting with access to physicians, which would allow continuing medical, social, and psychological support, rather than by direct-to-consumer genetic testing companies with little medical follow-up and support. Before any type of genetic test can be done, each individual to be tested needs to be fully informed about the consequences of these tests, including information about the disease itself, a-priori risk of inheritance, and consequences of these genetic tests for other family members.

If identification of a causal mutation in a patient with AD results in requests for pre-symptomatic genetic testing in other members of the family, this testing should be done only in the context of genetic counselling provided by teams with experience in neurodegenerative diseases. Such requests might come from family members with autosomal dominant AD, from individuals with a family history compatible with familial AD (the disease occurs in more than one individual, and at least two of the affected individuals are third-degree relatives or closer), or from individuals with an isolated case of sporadic AD.

When genetic testing is requested by a symptomatic individual, the patient should be accompanied by a family member or any declared representative. If the individual is pre-symptomatic, a protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended.²³⁶ This testing has several weaknesses. In autosomal dominant AD, the search for the causative mutation in a family will focus on *APP*, *PSEN1*, and *PSEN2*. However, half the families will not have any mutations in these three genes. Furthermore, due to the heterogeneity of clinical features in dementia, misdiagnosis of AD in the family has to be considered. In

	Deterministic genes	Susceptibility loci
Disease type	Rare	Common
Inheritance	Mendelian, monogenic	Complex, multigenic
Number of genes involved	Few (one)	Many
Prevalence of risk variant	Very rare (<1 per 10 000 individuals)	From rare to common
Test result	Highly predictive	Probabilistic
Individual impact	Strong	Weak
Family impact	High	Low
Potential population impact	Low	High
Risk	Simple (binary: yes or no)	Complex
Lifestyle factors	Do not affect risk in general	Modify risk

Adapted from Wright and Kroese.²³⁹

Table 7: Pre-symptomatic genetic testing for deterministic monogenic mutations and susceptibility loci

particular, the most common genetic cause of familial frontotemporal lobe dementia, an expansion of the *C9orf72* hexanucleotide repeat, has been identified in families in whom AD has been misdiagnosed.²³⁷ Thus, in families with a clear autosomal dominant inheritance pattern, the possibility of other causative genes should be considered, with an extension of the number of target genes if mutation screening has been requested. A post-mortem neuropathological examination in the family will also help to define the clinical diagnosis.²³⁸ Finally, in families who request genetic testing but lack mutations in the known genes, storage of DNA for future mutation screening in novel genes could be considered, since the risk of recurrence cannot be excluded.

Apart from the three causative genes, the other gene that could be tested for is the strongest susceptibility gene for AD, *APOE*. However, despite a high attributable fraction of the *APOE* $\epsilon 4$ allele in the general population (around 20%) and a high lifetime risk in homozygous carriers, the $\epsilon 4$ allele is neither necessary nor sufficient to cause AD. Thus, use of *APOE* genotyping to predict AD risk is not recommended because of its low sensitivity and specificity for diagnosis, the lack of preventive options, and the difficulty of estimating an absolute individual risk.

The genetic testing outcome of the presence of a disease mutation in deterministic genes such as *APP*, *PSEN1*, and *PSEN2* in early-onset AD is very different from a positive test result for a risk gene such as *APOE* or bridging integrator 1 (*BIN1*; appendix) in late-onset AD (table 7).²³⁹ Indeed, for deterministic mutations, the outcome is binary, either the mutation is present and the disease will unequivocally develop at some point in the future, or the mutation is absent and the early-onset form of AD will not develop. By contrast, the presence of a risk allele for a susceptibility gene will result in a lifetime risk-probability score for developing the disease in the future.²³⁹ In most situations, multigenic risk confers only a genetic susceptibility, which will be modulated in a favourable or unfavourable way by gene–gene and gene–environment interactions.

Ethical concerns in genetic testing

Despite the similarities between AD and other neurodegenerative disorders such as Huntington's disease, early diagnosis of a disease whose symptoms might appear years afterwards and for which no treatment is available raises important ethical issues that need to be anticipated. Doing clinical or prevention trials in pre-symptomatic individuals with autosomal dominant mutations or in asymptomatic individuals at risk of developing AD raises ethical questions, because genetic testing will disclose to the individual participating in the trial his or her risk status.

Some ethical concerns were addressed in clinical trials that examined the effect of *APOE* genetic susceptibility testing on asymptomatic individuals: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) studies.²⁴⁰ Results of the REVEAL trials suggested that disclosure of *APOE* genetic results by trained professionals using appropriate educational approaches does not generally result in short-term adverse psychological effects. However, these studies were not fully representative of a typical clinical setting. The participants volunteered for the study and they were preselected (had a parent with AD), highly educated, generally female, and received a free-of-charge test, the results of which were not included in their medical record. Nevertheless, these studies provide insight into what can be expected from the various all-in-one personal genomics services that report risk scores for health conditions and usually include results for AD susceptibility genes. Finally, early identification of pre-symptomatic individuals might have major psychological effects and other consequences, not only for the patient but also for family members who might be indirectly informed of their own risk.^{241–243}

The way forward in genetics

The discovery of causative *APP*, *PSEN1*, and *PSEN2* mutations in early-onset autosomal dominant AD paved the way for the amyloid cascade hypothesis of the disease.²¹⁴ Less than 20 years after the hypothesis was first published, expansion of the research landscape has been enabled by non-hypothesis-driven genomic approaches, such as whole-genome screening, providing an important entry point into AD research. The 40 genes and susceptibility loci identified so far, whether confirmed or suspected, offer insight into the high level of complexity that underlies the brain pathology of amyloid plaques and neurofibrillary tangles. However, these genetic discoveries now need to be taken forward. We have entered a post-GWAS era, in which all the research methods that are available in biological and computer sciences need to be integrated—bioinformatics, so-called omics technologies, systems biology, epigenetics, molecular and cellular studies, animal models, risk-factor assessments, and social-care and health-care research (figure 4). The future is transdisciplinary and will necessitate well planned and target-oriented

development of databases and biobanks that can harbour information from all areas of research and health care, including population-based studies, clinical data, and experimental research results.

In 2012, the USA launched a major sequencing programme in the context of the National Alzheimer's Plan, with the aim of sequencing 10 000 whole exomes and 600 whole genomes in selected patients with AD and healthy controls.²⁴⁴ Similar European initiatives have been launched in the context of research calls through the EU JPND. Following the example of the GWAS consortiums, sequencing consortiums are now being formed to enable data sharing. However, the magnitude of the information collected will require large data-handling infrastructures.

In parallel, the use of genomics in clinical research must be reinforced. Ready-to-use methods that allow rapid identification of genetic markers in patients attending memory clinics should be developed. These approaches could be used to aid differential diagnoses in dementia and other neurodegenerative disorders. Moreover, they would allow physicians and patients to be educated and prepared for precision medicine, the next revolution in clinical care. However, as long as no effective treatments are available for AD (and even after such treatments become available), social and ethical research must be strongly supported to help patients to cope with the notion of an increased lifetime risk of AD, and to protect them from any negative consequences (eg, access to employment or insurances) of early diagnoses given in the context of clinical research and health care.

To this end, greater efforts must be made in the European health-care systems to enable understanding of the genetic underpinnings of neurodegenerative diseases. To achieve this, professionals should be educated and families and patients should have universal access to qualified genetic counselling. In parallel with the progress in AD genetics and genomics, advances in the genetics of other neurodegenerative dementias, such as frontotemporal dementia, have led to similar challenges.²⁴⁵

Tackling AD is no longer in the hands of any one researcher, team, or even country. The first pilot EU JPND research was initiated in 2008. Geneticists and epidemiologists began to share data at the international level and, in less than 5 years, were able to discover more than 20 new AD susceptibility regions.²¹³ To speed up progress even more, this global collaboration must be extended to even more countries. The JPND initiative now includes 28 countries, including some non-European nations (eg, Canada, Israel). Awareness of the need for global collaborative research is growing, as shown by the G8 summit in London on Dec 12, 2013, which was dedicated to dementia. The ultimate goal is increased global collaboration and data sharing for the greatest benefit of our populations and economies.

For more on the US National Alzheimer's Plan see <http://napa.alz.org/>

For more on the REVEAL studies see <http://www.genomes2people.org/reveal/>

Summary and recommendations

The heritability of AD is estimated to be greater than 60%. Several specific gene mutations cause, or contribute to, early-onset familial forms. Gene variants that increase susceptibility to AD have also been identified and large-scale GWAS are in progress. Genetics plays a major part in understanding the mechanisms of AD and will have an important role in the implementation of prevention and care strategies in the future. Well organised biobanks and large collaborative groups that share data are essential to advance understanding of the genetic underpinnings of AD. Insights into the pathogenesis and clinical course of inherited early-onset disease might be generalisable to the development of therapies for sporadic, age-related dementias.

To optimise the use of genetics in the prevention of dementia, pre-symptomatic and early diagnosis of AD, and development and use of present and future treatment approaches, we make the following recommendations.

(1) Data sharing and large-scale national or international collaborative studies should be encouraged.

(2) Clinical and genetic interdisciplinary research should be initiated and supported to advance understanding of the complex and heterogeneous nature of neurodegenerative diseases.

(3) Guidelines are needed for health professionals to support the use of new genetic tests, including information about the clinical value of whole-genome and whole-exome testing (next-generation sequencing).

(4) A legal framework should be developed that regulates the use of personal predictive health information by third parties, protects individuals who undergo genetic testing and their wider family, and facilitates research.

(5) Efforts are needed to increase societal awareness and knowledge of the use and limitations of genetic testing and the ethical concerns associated with such testing.

(6) Genetic counselling should be provided for people who undergo genetic testing. Appropriately trained personnel should provide such counselling within an adapted and professional psychological support system (similar to the genetic counselling provided for Huntington's disease).

(7) Systematic searches should be developed for GWAS and next-generation sequencing data to identify causal variants and biological pathways associated with AD.

(8) DNA and clinical data should be systematically collected and stored in clinical settings, clinical trials, and prevention studies for post-hoc research studies.

(9) The role of gene–gene interactions and gene–environment interactions in disease pathogenesis and progression should be investigated.

(10) Functional studies are needed in the post-GWAS era to unravel the molecular mechanisms of associated genetic variants and the pathways that lead to pathology.

Section 5. Biology of Alzheimer's disease

In 1906, Alois Alzheimer described the pathological changes present in the brain of the first patient with AD, Auguste D. In the past 110 years, substantial knowledge has been gained about the genetic and environmental factors that contribute to the disease (sections 3, 4). However, what triggers the characteristic pathology of AD and which mechanisms drive the progression of the disease remain unknown. Understanding of the basic biology of AD pathogenesis and the way in which clinical dementia relates to the presence of amyloid plaques and tau tangles is urgently needed so that strategies for treatment and prevention can be focused on the correct disease target.

Amyloid β and tau as therapeutic targets

A distinctive feature of AD brain pathology is the accumulation of small (about 0.1 mm) spherical structures called amyloid plaques. These plaques are composed of fibrils formed by the protein fragment A β , and are surrounded by dysfunctional neurons. Different variants of A β exist; one of the longest forms, A β 42, is thought to be particularly toxic. The other major hallmark of the disease is the accumulation of tau protein inside neurons, forming fibrillary tangles. Amyloid plaques and tau pathology are present not only in AD, but also in several other neurodegenerative disorders, which suggest a central role for these proteins in neurodegeneration. For example, A β is accumulated in cerebral amyloid angiopathy²⁴⁶ and tau in frontotemporal dementia or Niemann-Pick disease.²⁴⁷

In the 1990s, studies of early-onset familial AD identified distinct mutations in *APP*, *PSEN1*, and *PSEN2*

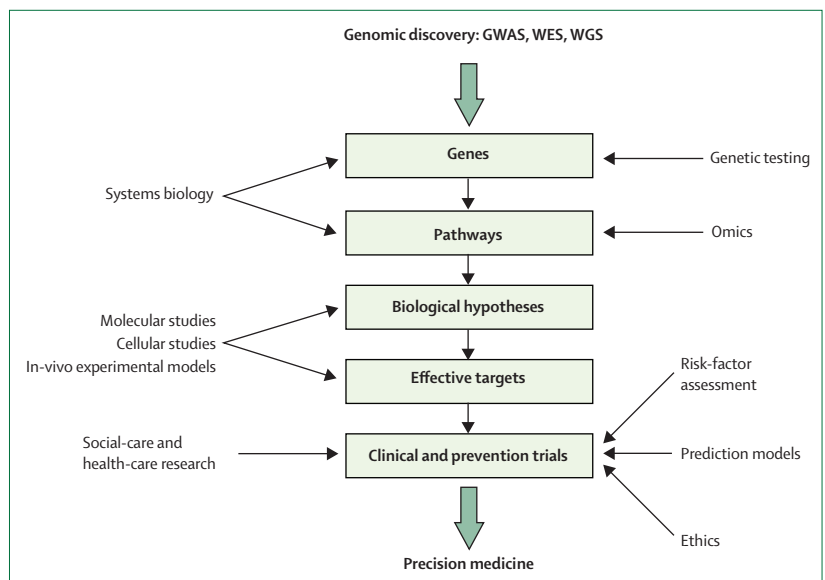


Figure 4: From genetic and genomic discoveries to precision medicine

Starting with genetic and genomic discoveries, future research studies need to integrate data from all research areas to construct testable hypotheses and draw meaningful conclusions about the functional consequences of the known Alzheimer's disease genes and loci. These integrated analyses could push the research frontier forward, allow personal risk profiles to be generated, and ultimately help to shape individualised strategies for intervention. GWAS=genome-wide association study. WES=whole-exome sequencing. WGS=whole-genome sequencing.

(section 4). The proteins encoded by these three genes are involved in the production of A β , and most (but not all) of the causative mutations cause an overproduction of A β peptides.^{248,249} These neuropathological and genetic observations led to the amyloid cascade hypothesis, which posited that A β initiates a molecular cascade of toxic effects that lead to neurodegeneration and subsequently to the clinical manifestations of dementia.²¹⁴ Some forms of A β (A β 42 or A β 43) are now believed to be trigger factors for AD,²⁵⁰ although which conformational structure (fibrils,²⁵¹ oligomers,²⁵² soluble forms,²⁵³ or dimers²⁵⁴) of these peptides drives neurotoxicity is still debated.

The amyloid hypothesis has dominated the debate about the cause and pathogenesis of AD, and has guided efforts to find treatments (section 7). Although the mechanisms by which the rare mutations in *APP*, *PSEN1*, and *PSEN2* lead to excessive A β generation are now well understood, the precipitating factors that lead to A β accumulation in the much more common sporadic forms of AD are still unknown, although they probably result from a combination of environmental factors and risk genes. Despite the narrow focus on amyloid in AD, A β plaques are ubiquitous in people older than 70 years and about 30% of healthy aged-matched individuals have as much plaque load in their brains as do typical cases of AD.²⁵⁵

Following the amyloid cascade hypothesis, explanations have been proposed for the link between A β and tau pathology in pathogenesis (figure 5). However, the mechanistic relation is not yet clear, because transgenic animals that carry genes for familial AD and express large amounts of A β have little or no tau tangle pathology. The biological functions of APP, the protein precursor of A β , and its metabolites, including A β , in the healthy individual also need to be explained. Thus, the potential risks of targeting A β production for the treatment of AD (in the brain and the periphery) are as yet undetermined.

A β is an antioxidant,²⁵⁶ has antimicrobial activity,²⁵⁷ activates other signalling proteins,^{258–260} and modulates cholesterol transport,²⁶¹ but its biological role is largely unknown. β -secretase (including the form known as β -site APP-cleaving enzyme 1 [BACE1]) and γ -secretase are the enzymatic proteins that result in A β generation, so efforts have been made to develop inhibitors of these proteins for clinical use. However, these enzymes seem to have roles in the metabolism of multiple substrates, which complicates efforts to achieve selectivity to inhibit only A β production. Some of these substrates are fundamental to normal cell biology. For example, BACE1 cleaves β -subunits of voltage-gated sodium channels²⁶² and neuroregulins, which are crucial for neuronal development and myelination^{263,264}—processes that are important not only during development but also in adult life, particularly for the reparation of neuronal damage.

Similarly, γ -secretase is a promiscuous enzyme that cleaves more than 90 protein substrates and regulates various cellular events, such as cell-fate determination,

adhesion, migration, neurite outgrowth, axon guidance, and the formation and maintenance of synapses.²⁶⁵ Besides APP, the most-studied γ -secretase substrate is Notch, a signalling molecule that is crucial for development and cell-fate determination. Development of drugs that can inhibit γ -secretase has not been an issue, but selectivity to inhibit only APP cleavage is difficult to achieve. In addition to decreasing the production of A β , γ -secretase inhibitors affect many other proteins and the production of other functionally important peptides, with potentially toxic consequences. Therefore, new strategies are needed to develop drugs that selectively inhibit γ -secretase cleavage of APP without affecting other substrates. These efforts received a boost from the discovery of modulators that control γ -secretase cleavage of specific substrates by binding and recruiting them to γ -secretase for processing—small molecules capable of reducing A β 42 production without affecting other functionally important γ -secretase products.²⁶⁶

Inhibition of the enzymes that produce A β also has consequences for the metabolism of APP, which can affect the production of other APP metabolites (eg, soluble APP or the APP intracellular domain [AICD]). AICD has more than 20 interacting protein partners that regulate important signalling pathways and cell functions, such as transcription, apoptosis, and cytoskeletal dynamics.^{267,268} Roles for APP have been described in cell migration,²⁶⁹ trafficking, and signalling;²⁷⁰ neuronal calcium homeostasis, synaptic transmission, and networking;²⁷¹ and neurotrophic mechanisms.²⁷² Thus, targeting APP processing to reduce A β concentrations could have many biological consequences. Clinical trials of drugs that target A β production have not reached their primary clinical endpoints and have, in some cases, caused serious side-effects (section 7).

An alternative way to reduce A β concentrations is to increase A β clearance from the brain. Since the absence of A β does not lead to any loss of physiological function in mice,²⁷³ the elimination of this peptide could be a safe approach for treatment, but whether clearance of this peptide has any benefits in patients with symptoms of AD, such as slowing down disease progression, remains to be seen. Some anti-amyloid immunotherapeutic approaches have been tried in patients with AD, with disappointing results.²⁷⁴ Thus, the question of whether A β (production or clearance) is a good target for treatment is still unknown, and efforts are needed in basic research to understand the possibilities and limitations of this approach.

The other distinguishing feature of AD, the formation of tau tangles in brain neurons, has historically been regarded as a secondary player in disease pathology, despite its direct correlation with neuronal death and disease progression.²⁷⁵ By contrast with the *APP* gene, mutations in the microtubule-associated protein tau (*MAPT*) gene do not cause AD, but do cause familial frontotemporal dementia.²⁷⁶ Some biological functions of

tau are well known—the protein regulates microtubule assembly, dynamics, and spatial organisation, and participates in the axonal transport of organelles and vesicles.²⁷⁷ The biological activity of tau is regulated by its degree of phosphorylation, and tau in neurofibrillary tangles is abnormally hyperphosphorylated.²⁷⁸ Hyperphosphorylation converts tau from a microtubule-stabilising to a microtubule-disrupting protein.²⁷⁹ Evidence strongly suggests that neurodegeneration in many tauopathies results from loss of the biological function of tau, together with the initiation of toxic events. Hyperphosphorylation promotes the aggregation of tau into paired helical filaments, leading to the formation of tangles inside neurons and corresponding impairments of neuronal cytoskeletal organisation and of the transport of proteins and organelles.

Efforts have been made to develop inhibitors of the enzymes, tau kinases, which phosphorylate the protein. However, several kinases are involved in the generation of hyperphosphorylated tau, raising the question of whether specific or multiple tau-kinase inhibitors would be more effective as potential treatments for AD.²⁸⁰ Individual tau-kinase inhibitors, mainly glycogen synthase kinase 3 β (GSK3 β) inhibitors or lithium, successfully reduce tau pathology in animal models of AD.²⁸¹ However, the GSK3 inhibitor tideglusib failed to meet the primary cognitive endpoint in a 26 week phase 2b trial in more than 300 patients with mild-to-moderate AD.²⁸²

As an alternative to kinase inhibition, activation of phosphatases has been proposed as a strategy to reduce tau phosphorylation. Protein phosphatase 2A (PP2A), the main brain phosphatase involved in the dephosphorylation of tau, has received special attention. Treatment of tau transgenic mice with the PP2A activator sodium selenate reduced tau hyperphosphorylation and tangle formation, improved memory, and prevented neurodegeneration.²⁸³ However, PP2A has multiple substrates, which might lead to multiple side-effects, and the activation of this enzyme to reduce tau phosphorylation specifically is not an easy task.

Several other anti-tau treatments effectively prevented or intervened in the process of tau hyperphosphorylation in animal models, thereby improving neuronal function or cognition. For example, the microtubule-stabilising drug davunetide showed promise in preclinical studies,²⁸⁴ but a 12 week placebo-controlled study of intranasal davunetide failed to show significant benefits in 144 patients with amnesic mild cognitive impairment.²⁸⁵

Other anti-tau strategies, such as tau anti-aggregants or tau immunotherapy, are being tested in preclinical and clinical studies (section 7). Among them are methylene blue (methylthioninium chloride), a drug identified in 1891 as a possible anti-malaria agent,²⁸⁶ which might inhibit tau aggregation.²⁸⁷ Efforts are being made to design an effective vaccine against tau pathology, but few studies of passive immunisation (transfer of ready-made

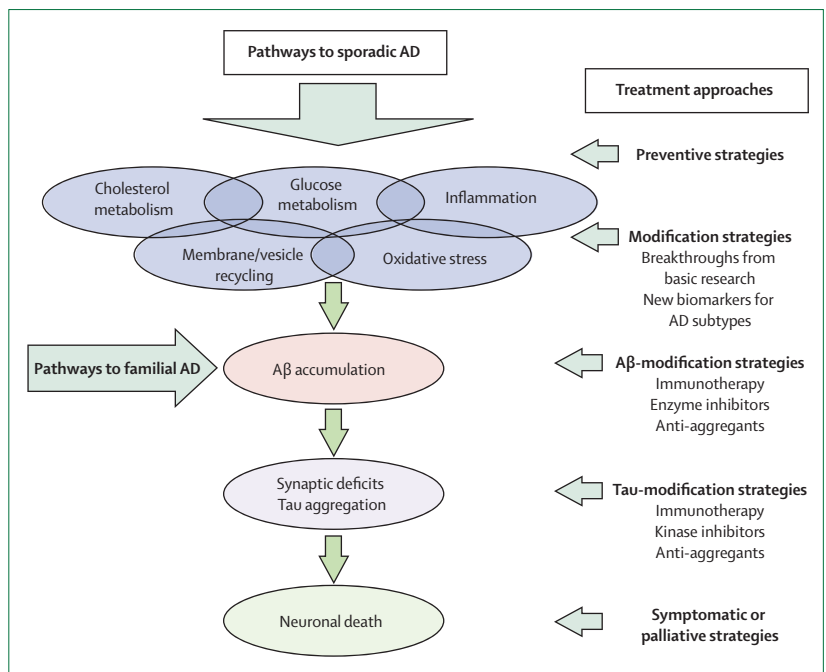


Figure 5: Pathways to Alzheimer's disease

Epidemiological and genetic studies of people with non-genetically determined (ie, sporadic) AD have identified mechanisms that might underlie brain A β accumulation, neuronal tau hyperphosphorylation, and synaptic deficits, ultimately leading to cognitive impairment and dementia. In familial AD, the disease begins with A β pathology. It seems likely that different causative pathways result in distinct disease subtypes, which should be treated differently. The identification of subtypes of patients, with homogeneous pathogenesis and prognosis, will facilitate research and result in more accurate and personalised treatments for sporadic and familial AD. AD=Alzheimer's disease. A β =amyloid β .

antibodies against a target protein to enhance its clearance) against tau protein are in progress.²⁸⁸ Several studies suggest that active immunisation (induction of immunity after exposure to an antigen—the recipient develops antibodies that can be stored permanently) might be effective against tau in animal models.²⁸² As for anti-amyloid approaches, several key questions remain to be answered in relation to tau-based immunotherapeutic approaches. The exact species to be targeted (aggregation states, fragments, and subtypes of tau) and the mechanisms by which antibodies clear target molecules are unknown.

Whether current anti-tau immunotherapeutic approaches will be effective in patients or lost in translation, as has been the case for many previous strategies targeting A β , remains to be seen.

The reasons for the lack of successful translation from preclinical to clinical studies in treating AD are unknown. For both A β -based and tau-based approaches, the scarcity of good predictive animal models, good biomarkers for disease progression, and well-defined target populations in clinical trials have been major challenges in demonstrating potential benefits in AD. The use of simple animal models that reflect a single aspect of AD might not be enough to capture the complexity of the disease and develop new treatments.

Animal models of AD

Transgenic animals, in which genetic engineering techniques are used to mimic some aspect of the disease, are important for studies of the molecular basis of neurodegenerative disorders and the mechanisms of disease progression. Many organisms, including mice, zebrafish, worms, and fruit flies, have been used to model aspects of AD. Most of these models are based on the overexpression of one, two, or in some cases several human mutations that result in the accumulation of A β or hyperphosphorylated tau in the brain. Despite many promising results in animal experiments, drugs that have made it to human clinical trials have so far failed to reach the primary objectives of these studies, and have in some cases had serious adverse effects. Thus, although existing animal models can be highly informative about the molecular processing of A β and tau, they do not fully capture the pathophysiology of sporadic AD in humans.

Despite some efforts to generate disease-relevant experimental animal models,^{289,290} new models of AD are urgently needed for drug development. Some inherent problems exist with transgenic mice models: the foreign gene is inserted at unknown locations in the genome and other genes could be disrupted, non-natural promoters of gene transcription (the first step in gene expression) are used, and gene expression (the synthesis of a functional gene product) is unnaturally high. A knock-in mouse has been developed in which the endogenous mouse *App* gene is substituted with a human version of *APP* carrying a familial AD mutation. The main advantage of these mice compared with previous mouse models is that they show ageing-dependent amyloid pathology, neuroinflammation, synaptic alterations, and memory impairment, all in a manner more like the human disease.²⁹¹ However, these mice do not develop tau pathology, and although they offer promise for future studies of amyloidosis (accumulation of A β in brain tissue), they still have weaknesses as a model of AD.

Research breakthroughs are needed for the development of animal models that recapitulate the complexity and heterogeneity of the disease. Such models of AD will be crucial not only in testing potential treatment approaches, but also in advancing understanding of basic disease biology.²⁹² One possibility is that, in most cases of AD, A β and tau pathologies are endpoints of other disease-driving mechanisms that have not been captured in animal models. Thus, successful inhibition of A β or tau pathologies might not necessarily mean finding a successful drug for AD. In view of the heterogeneity of AD, a multi-target approach will probably be necessary.

Mechanisms of AD

Epidemiological evidence emphasises the importance of vascular health and diabetes in the development of sporadic AD, and hypertension and high blood cholesterol

concentrations have been shown to increase risk in many studies (section 2).²⁹³ Additionally, several other pathways have been identified that can contribute to disease development, such as mild TBI,²⁹⁴ ischaemia and hypoxia,²⁹⁵ neuroinflammation,²⁹⁶ environmental toxin β -N-methylamino-L-alanine from cyanobacteria,²⁹⁷ and metabolic abnormalities associated with decreased brain glucose uptake.²⁹⁸ Although, at present, the use of risk indicators increases the reliability of predicting who will develop AD only slightly, their greater importance is that they identify pathways and processes that lead to AD. Large GWAS and systematic exome-sequencing approaches have confirmed some of the previously known pathways and have identified new pathways (section 4). However, the new susceptibility loci have only moderate effects on risk (with ORs in the 1.1–2.0 range).²⁹⁹ Analyses with pooling of larger numbers of samples might provide further insight into the pathways leading to AD.

In broad terms, GWAS identified cholesterol metabolism, the innate immune system, and endosomal vesicle recycling as important contributors to AD. The strongest known genetic risk factor for sporadic AD is the presence of the $\epsilon 4$ allele of the cholesterol carrier APOE (section 4).²⁰² Since the discovery of the APOE4 protein as a major risk factor for AD, efforts have been made to link this molecule to A β metabolism, aggregation, and deposition. Increased plaque deposition has been noted in individuals with APOE4 and in animal models of brain amyloidosis.³⁰⁰ APOE4 can potentiate A β toxicity in vitro^{301,302} and in animal models,³⁰³ and it has been suggested that A β clearance is less efficient in carriers of the APOE $\epsilon 4$ allele.³⁰⁴ By contrast, the contribution of APOE4 to tau pathology remains poorly understood.

Reduced capacity for neuronal delivery of cholesterol in APOE $\epsilon 4$ allele carriers is thought to have consequences for the development of new synapses and for neuronal repair mechanisms. The brain is the major cholesterol-containing organ in the body,³⁰⁵ and efficient cholesterol metabolism is crucial for recovery of damaged membranes. Furthermore, neuronal axons are surrounded by cholesterol-rich myelin, which protects axons and facilitates neurotransmission. Thus, impaired cholesterol synthesis, delivery, or metabolism is likely to contribute directly to disease progression.³⁰⁵ This notion is supported by GWAS, in which genes related to cholesterol synthesis, transport, uptake, or metabolism were shown to be linked to AD (eg, ATP-binding cassette subfamily A member 7 [*ABCA7*], *ABCA1*, clusterin [*CLU*], and cytochrome P450 family 46 subfamily A member 1 [*CYP46A1*]).²⁹⁹ However, further efforts are needed to understand the mechanisms by which APOE4 and other cholesterol-related molecules contribute to AD pathology, and to clarify whether experimental manipulation of brain cholesterol metabolism has therapeutic potential.

Studies in the late 1980s suggested a role for the innate immune system and the complement cascade (part of the

immune system that helps antibodies and phagocytic cells to clear toxins or pathogens) in the pathogenesis of AD,³⁰⁶ and inflammation has been proposed as an early pathogenetic event in the disease.³⁰⁷ The brain has its own innate immune system, which can maintain a low-grade, systemic inflammatory reaction. Presumably, the innate immune system of the brain has a defensive, protective role, but a chronic inflammatory process might damage neuronal cells. The brains of patients with AD harbour activated immune cells (microglia and macrophages) and various proteins that result from inflammatory reactions. Proteins of the classic complement cascade might also be of particular importance, because studies have shown that they are largely expressed in the cortical pyramidal neurons, which are severely affected in AD.³⁰⁸ However, whether complement-producing neurons are particularly vulnerable to immune-system attack is unknown. GWAS have clearly shown that variability in innate immunity confers risk for AD.^{208,209} The S isoform of the complement component receptor 1 (CR1) protein, has been associated with AD²¹² and might be linked to increased complement activation.³⁰⁹ Furthermore, the complement cascade is activated by A β ,³¹⁰ which would stimulate phagocytic mechanisms to remove A β deposits. If this process were to fail, persisting complement activation would cause excessive inflammation that could damage neurons.

Another inflammation-associated gene uncovered by exome sequencing in AD is *TREM2*.²²³ *TREM2* suppresses the inflammatory response in microglial cells,³¹¹ and it might participate in the regulation of phagocytic processes to remove amyloid.³¹² Thus, loss of function of *TREM2* might result in chronic inflammation and amyloid accumulation. *APOE* has been identified as a ligand for *TREM2*,³¹³ but the biological consequences of this association and its relation to AD pathology remain to be defined. Despite the links between inflammatory and immune components of AD pathology, the mechanisms by which they affect the onset of amyloid deposition and tau phosphorylation need to be elucidated. Longitudinal data are missing, and since inflammatory responses can have both beneficial and detrimental effects, to understand how to regulate inflammation effectively is an important challenge for AD research.

GWAS approaches have also identified endosomal vesicle recycling as one of the pathways in AD pathogenesis.^{208,209} Endosomes are a dynamic vesicular network that provide an environment for material to be sorted in a cell before it is degraded. Some material from endosomes is recycled to the plasma membrane of cells, and *SORL1*, phosphatidylinositol-binding clathrin assembly protein (*PICALM*), and *BIN1* all probably have a role in this process. Little is known about the functional implications of this discovery. However, it is worth noting that some of the metabolism of APP occurs in the endosomal pathway,³¹⁴ and impairments in the machineries used to secrete or degrade unwanted proteins could plausibly affect the survival of neurons.

Another hypothesis is that AD has a prion-like pathology. According to this model, A β or tau,³¹⁵ misfolded or aggregated, is produced in one cell, secreted to the extracellular space, and gains entry into neighbouring connected cells, where it triggers further A β or tau aggregates. Thus, A β and tau inclusions begin in specific regions of the brain and are spread to other areas.^{316,317} Intracerebral or intraperitoneal injections of A β or extracts from the brains of patients with AD induce brain amyloidosis in animal models.^{316,317} In 2015, Jaunmuktane and colleagues³¹⁸ reported an autopsy study of individuals who received human cadaveric supplementary pituitary hormone when young, and showed brain A β pathology at the age of death (36–51 years). The authors suggest that cadaveric pituitary hormone could contain “seeds” of A β that transmitted the pathology. Further research is necessary to clarify the mechanisms and possible risks associated with transmissible A β or tau.

Consensus exists among researchers that A β aggregation and accumulation is the cause of familial AD. However, this view is not consensual for sporadic AD. A β is important in the pathology of such cases, but might not be the cause of AD. The identification of multiple pathways to AD is a mark of the heterogeneous causes of the disease. To discern which overlapping, intersecting, or synergistic mechanisms in these pathways induce brain A β and tau pathology remains an important challenge for the future.

Future goals

Despite impressive efforts in the past three decades, the causal mechanisms of AD remain to be elucidated. Furthermore, the assumption that molecular mechanisms that underlie genetically determined forms of the disease are identical to those resulting in late-onset AD needs to be tested. Non-European initiatives such as the API study (of a kindred carrying a mutation in *PSEN1*) and the DIAN study (of individuals with mutations in *APP*, *PSEN1*, or *PSEN2*)²³⁴ will determine, in the near future, whether clearance of A β from the brain is effective in the treatment of familial AD (section 7). One possibility is that targeting A β will be successful only for these autosomal dominant forms of AD, in which increased A β production occurs from birth. For most AD cases, amyloid accumulation is probably a later event that results from other metabolic disruptions. We have substantial information on different pathways that contribute to the disease, and a priority for the future is to discern the causative forces and overlapping mechanisms among them, and to determine how these mechanisms result in (or from) A β accumulation and tau hyperphosphorylation.

The identification of subtypes of patients with disease of homogeneous aetiology (cause or pathogenesis) and prognosis will enable the development of more effective, personalised treatments. Intensification of innovative basic research will also result in the identification of new

biomarkers for the subtyping of AD (section 6), which will open possibilities for precise medical interventions (figure 5).

Summary and recommendations

The brain pathology of AD is distinct from that of other neurodegenerative diseases. Amyloid plaques are made up of deposits of A β , a derivative of the precursor protein APP, and neurofibrillary tangles result from the abnormal accumulation of a protein called tau. Most therapeutic strategies for AD are focused on the direct reduction of these protein deposits, or on other proteins and enzymes that regulate their concentrations in the brain. However, epidemiological and genetic studies have identified a range of factors that contribute to AD, including insulin resistance, hypertension, deficits in cholesterol transport, and neuroinflammation. Improved understanding of the mechanisms that link these factors to A β and tau pathways, and how clinical dementia relates to the presence of amyloid plaques and tau tangles, is urgently needed so that prevention and therapy can be focused on the correct disease targets.

Preventive strategies to target risk factors for AD are likely to be successful in delaying by a few years the onset of disease. However, in an ageing population, the need to find a cure or an effective therapy for AD is imperative. Without new breakthroughs in understanding the basic biology of disease pathogenesis, the development of a cure seems unachievable. We make the following recommendations.

(1) Identification of novel disease-modifying strategies (ie, thinking outside the box) needs to be intensified. A strong commitment to the support of innovative basic research is needed to advance understanding of the biology of AD—a prerequisite for the identification of new, valid targets and the development of new treatments.

(2) Efforts to understand disease mechanisms need to be expanded, encompassing systems biology, vascular research, neuroplasticity, and inflammation. Programmes that support multidisciplinary, collaborative studies should be encouraged.

(3) Relevant animal models of AD need to be developed to study disease mechanisms and to test potential new treatments. Understanding of the biology of AD is increasing rapidly, and new models should aim to capture the complexity and heterogeneity of the disease. Specific lines of support should be provided for the development of relevant animal models, with a view to accelerating therapeutic development.

Section 6. Diagnosis and clinical assessments in Alzheimer's disease

The consequences of a diagnosis of AD for patients and their families are complex. AD is one of the diseases most feared by the general public, and the disclosure of a dementia diagnosis can result in severe mental distress, with evidence of an increased risk of suicide after

diagnosis.³¹⁹ However, with the right approach, evidence suggests that a diagnosis can relieve symptoms of anxiety in patients because it explains a frightening loss of cognitive capacities.³²⁰ At more advanced stages of AD, self-reflection is often impaired and the meaning of the dementia diagnosis might not be understood fully by the patient, which prevents severe mental distress. For caregivers, the disclosure of an AD diagnosis is also stressful and associated with fear and grief, but it can trigger seeking and receiving of help to cope with the situation.

Overall, the process of providing information on diagnostic procedures and the meaning of outcomes, applying and interpreting diagnostics, disclosing the diagnosis, and providing counselling on prognosis and treatment options is a very complex and individualised procedure, which is becoming even more complex with earlier diagnosis and the increasing availability of new biomarkers and treatment options. This complexity increases demands on the diagnosing physician and requires increased specialist knowledge.

Health services and professionals involved in diagnosis

The services and professionals involved in dementia diagnosis in different European countries depend on the health-care system and the reimbursement structure. In many countries—eg, Germany—a large proportion of patients with AD is seen only by general practitioners (GPs), and a diagnosis is often not firmly established. Some patients are referred to neurologists or psychiatrists in private practice, but only a very small proportion of patients is diagnosed in specialised centres, such as memory clinics, which are usually linked to large hospitals and universities. No specific reimbursement structure exists for guideline-based dementia diagnosis.

Several EU countries now have national plans or guidelines for dementia diagnosis, the chain of care, and recommended treatment. In the UK, policies to increase the recognition of dementia have introduced limited screening (linked to reimbursement for diagnosis) into hospitals and some dementia practices. However, the introduction of such policies without trial evidence of benefit has been controversial and, some would argue, has led to further delays in access to diagnostics services because of the large volume of referrals.

Benefits of a dementia diagnosis

Diagnosis of a dementia syndrome and clinical diagnosis of AD are usually the basis for pharmacological and non-pharmacological treatment, and can provide access to support for the person with dementia and their caregivers. Especially in younger people, differential diagnosis of the cause of dementia will be important for treatment decisions and estimation of individual prognosis. In older people, in whom most dementia is mixed (eg, co-occurrence of AD with other causes of cognitive decline), this differential diagnosis

is arguably less helpful. Rarely are fully reversible causes of cognitive decline detected, but most guidelines do highlight those that should be ruled out, such as hypothyroidism.

Diagnosis and clinical assessments: challenges and priorities

In the absence of substantial improvements in quality of life and effective treatments for people with dementia, there might be few incentives for family doctors to pursue a diagnosis of AD. However, patients and their families can benefit if a diagnosis is made appropriately and continuing care and support are made available.

AD is a slowly evolving disorder with a long preclinical period, followed by a prodromal phase with mild symptoms before the dementia stage is reached. At present, the clinical diagnosis of AD in clinical care and in most clinical trials is made at the dementia stage. Overlapping but slightly different sets of criteria for AD dementia are provided by the *International Classification of Diseases*, tenth revision (ICD-10),³²¹ which is used in Europe, and the *US Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).³²² These criteria list clinical features needed to make the clinical diagnosis of typical AD, such as memory deficit at initial presentation and slowly progressive onset and disease course. They also acknowledge atypical presentations of AD, such as the language variant (logopenic aphasia), the visuospatial variant (posterior cortical atrophy), and the variant with executive dysfunction (frontal variant).

The reliability of criteria has been established in clinical settings (ie, different physicians agreed reasonably well when applying the same set of criteria to the same patients).³²³ However, people with a clinical diagnosis of AD, when followed to post mortem, do not always have AD-type pathology, with around 20% suggested to be misclassified during life in one report.³²⁴ Also, many older people who fulfil neuropathological criteria for AD do not have dementia when they die, creating a continuing and largely unaddressed conundrum for the specialty of AD and early detection.

Research diagnostic criteria include the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria, the National Institute on Aging–Alzheimer's Association (NIA–AA) criteria, and the revised criteria of the International Working Group (IWG-2). Two major conceptual changes in recent years have been the introduction of biomarkers in combination with clinical syndrome definitions to the NIA–AA^{325–327} and IWG^{328–330} criteria, and the inclusion of criteria for pre-dementia stages of AD, which can be diagnosed on the basis of mild symptoms plus biomarkers or even in the absence of symptoms on the basis of biomarkers alone (table 8). These approaches are being applied in research, including validation studies and clinical trials

in dementia, and although not yet used in clinical practice, they will be adapted for clinical use in the future.

The main challenge in the clinical assessment of patients with AD is the transfer of concepts and methods that were developed mainly for advanced dementia to earlier stages of the disease. The focus on pre-dementia stages is crucial, because future treatments will probably have to be initiated at early stages to be effective (section 7). This transition can be achieved by viewing AD as a slowly progressive disorder of cognition that starts gradually before full dementia is reached. Identification of very early symptoms of disease, the effects of treatment on these symptoms, and predictors of treatment outcomes at the very mild symptomatic stage are urgent priorities. Recognition of the very early stage of AD as a disorder with distressing impairment of memory that affects the patient's wellbeing even in the absence of severe impairment in daily functioning is also important.

At present, the standard instruments used in clinical care and clinical trials include comprehensive and detailed cognitive test batteries, rating scales of functional impairment, informant-based questionnaires about IADL and basic ADL, and assessments of neuropsychiatric symptoms, quality of life, and disease-related burden. Most methods have been developed for the assessment of patients with dementia between the mild and the severe stage. Even though these measurements are widely accepted and understood in terms of their performance in clinical and population settings, they are acknowledged as being somewhat insensitive for people with high levels of education. Furthermore, such instruments sometimes lack sensitivity for very mild symptoms of the disease. Many measurements as applied will have uncertain reliability (ie, the same result might not be achieved when applied several times in the same person).

Cognitive assessment

Three main challenges exist with regard to improved assessment of cognition. First, it is common in clinical practice and clinical trials to describe the cognitive performance of patients with a single global score: the commonly used MMSE expresses the level of cognitive performance with a single number ranging from 0 to 30, and the standard scale for cognitive testing in clinical trials, the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog), expresses cognitive function as a single number between 0 and 70. This approach needs to be extended, especially for use in clinical trials, by measuring individual components of cognition (eg, memory, attention, language) to increase understanding of how these components are affected over time by the disease, how they relate to biomarkers as indicators of AD pathology, and how they individually respond to treatment. This information would also be of use in describing clinical subtypes.

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	NIA-AA criteria ³²⁵⁻³²⁷	IWG criteria ³²⁸⁻³³⁰	Comments
Diagnosis in the absence of symptoms	Preclinical AD: Stage 1: asymptomatic cerebral amyloidosis (CSF A β or amyloid imaging) Stage 2: asymptomatic cerebral amyloidosis with evidence of neuronal injury (volumetric MRI, CSF tau, or ¹⁸ F-FDG PET) Stage 3: cerebral amyloidosis with evidence of neuronal injury and subtle cognitive decline	Asymptomatic at risk: Normal cognition with one pathophysiological marker of AD (CSF A β and tau or P-tau, or amyloid imaging) Pre-symptomatic AD: Normal cognition with an autosomal dominant AD-causing mutation	The disease process, including accumulation of amyloid and tau pathology, can begin years or decades before symptoms emerge. The NIA-AA criteria specify three stages of preclinical AD, whereas the IWG criteria specify two different conditions in cognitively healthy individuals
Diagnosis of cognitive impairment due to AD (prodromal stage)	MCI due to AD—high likelihood: Biomarkers of amyloidosis (CSF A β or amyloid imaging) and neuronal injury (volumetric MRI, CSF tau, or ¹⁸ F-FDG PET) present MCI due to AD—intermediate likelihood: Biomarker of amyloidosis or neuronal injury present MCI—possibly due to AD: Biomarkers gave conflicting results MCI—unlikely due to AD: Biomarkers of amyloidosis and neuronal injury absent	Prodromal AD: Amnesic syndrome of the hippocampal type or a specific phenotype compatible with atypical AD, with one pathophysiological marker of AD (CSF A β and tau or P-tau, or amyloid imaging)	The IWG-2 criteria propose a specific type of memory impairment for AD and a confirmation of the diagnosis by biomarkers. The NIA-AA criteria do not propose a specific type of cognitive impairment in MCI and discuss different biomarker patterns in terms of different likelihoods of the presence of AD.
Diagnosis of dementia due to AD	Probable AD dementia: AD dementia with documented clinical decline AD dementia with an autosomal dominant AD-causing mutation Possible AD dementia: AD dementia with an atypical course AD dementia with evidence of mixed aetiology Probable AD dementia with evidence of the AD pathophysiological process: High likelihood of AD aetiology (biomarkers of amyloid abnormalities and neurodegeneration present) Intermediate likelihood of AD aetiology (biomarker of amyloid abnormalities or neurodegeneration present) Possible AD dementia with evidence of the AD pathophysiological process: High likelihood of AD aetiology (biomarkers of amyloid abnormalities and neurodegeneration present) Intermediate likelihood of AD aetiology (biomarker of amyloid abnormalities or neurodegeneration present) Pathophysiologically proved AD dementia: Clinical phenotype of probable AD with neuropathology findings indicative of AD	AD dementia: Episodic memory impairment or atypical AD phenotype with impaired activities of daily living and a pathophysiological marker of AD (CSF A β and tau or P-tau, or amyloid imaging)	The IWG criteria view the disease as a clinicobiological entity, so a diagnosis of AD dementia can be made in patients with typical or atypical clinical features only if a pathophysiological marker of AD is present

These research criteria are important in establishing a very early diagnosis of AD and in defining participants for clinical trials. After sufficient validation, these criteria could provide the basis for early, pre-dementia AD diagnosis in clinical practice. NIA-AA=National Institute on Aging–Alzheimer's Association. IWG=International Working Group. AD=Alzheimer's disease. CSF=cerebrospinal fluid. A β =amyloid β . MRI=magnetic resonance imaging. ¹⁸F-FDG PET=¹⁸F-fluorodeoxyglucose positron emission tomography. P-tau=phosphorylated tau. MCI=mild cognitive impairment.

Table 8: Classification of Alzheimer's disease subtypes across NIA-AA and IWG criteria

The second main challenge is detection of the earliest symptoms and symptomatic changes below the detection threshold of tests used at present. Several studies have described decline in different cognitive domains at the preclinical stage in individuals at risk of AD.³³⁰ However, measures of such changes have not been standardised and are not applied on a large scale across studies. Furthermore, they are not being tested in all the different patient groups to which they might be applied in the future (eg, patients in GP practices or memory clinics). New tests will need to incorporate techniques that allow reliable detection of the very subtle early changes in AD.

Subjective cognitive decline (SCD), which is defined by the experience of worsening of cognitive abilities, is often reported by elderly people.³³¹ It is associated with increased risk of progression to dementia in population studies.^{332,333} Some studies have shown that subjective cognitive decline adds predictive power about the risk of future dementia in an individual of a similar magnitude

to that provided by impairment in performance on a memory test.³³⁴ People with SCD are reported to have biomarkers that indicate the presence of AD pathology, such as reduced concentration of A β 42 or increased concentration of tau in the CSF,³³⁵ or AD-typical changes on brain imaging.^{336,337} Those with SCD and evidence for AD pathology measured by CSF biomarkers are at increased risk of dementia.³³⁸ According to a 2014 international consensus publication,³³¹ research is needed to develop improved and standardised assessments of SCD, and to investigate the relation of SCD to objective decline in cognition and psychiatric disorder such as depression and anxiety.³³⁹

The third main challenge is the minimisation of intra-individual and inter-individual variance and rater-related or rating-related confounds in cognitive assessments. Intra-individual variance refers to the fact that, in some tests, the performance of an individual changes from day to day (eg, because of differences in alertness or concentration) and is subject to learning

effects when the test is repeated (repetition effect). Problematic inter-individual variance can occur—eg, in the case of a verbal recall test that aims to assess memory, in which individuals with greater language abilities might have an advantage over those with poorer skills.

The rater-related or rating-related confounds describe the observation that patients score differently on a test depending on how it is administered (eg, in terms of task instructions), but also with regard to behaviour of the person who is doing the test (the rater). In particular, at the early disease stage (the late asymptomatic at-risk stage and the early prodromal AD stage),³³⁰ the decline in cognitive performance is small and often cannot be detected, because the normal day-to-day variation in performance on a particular test is larger than the subtle decline related to early AD. Thus, tests with less variation need to be developed as a matter of urgency. These tests should have standardised task instructions to reduce rating-related confounds and should minimise components that increase inter-individual variance (eg, being independent of language skills). Intra-individual variance can be reduced by applying the test without repetition effects.

Functional assessment

ADL scales have low sensitivity for early functional changes in the course of AD. However, early cognitive impairment can affect IADL at the pre-dementia stage of the disease, and IADL impairment actually predicts decline to dementia.³³⁴ At present, some diagnostic criteria acknowledge the presence of mild impairment of IADL and define the threshold for dementia by a level of impairment that interferes with independence. Because mild impairment already contributes to disease burden in affected individuals, improved assessment of IADL is needed, as are studies to examine the impact of early interventions on ADL impairments to establish whether such approaches have effects that are relevant and meaningful for patients. Current scales for IADL impairment in very early AD rely largely on observations reported by the informant. Innovative IADL assessments therefore need to include direct measures of the time taken and number of errors made by the patient while performing IADL.^{340,341}

Closely associated with IADL assessment is the approach of individualised outcomes of treatment, in which specific IADL (eg, using a telephone) are identified and defined with each patient as a goal of treatment (goal attainment), rather than applying an identical scale to all patients.³⁴² This approach is appealing because it focuses on the most relevant areas of impairment for the individual patient. It also mirrors clinical practice, in which patients discuss and work on individual goals with the treating physician. However, standardisation of the goal-attainment approach for clinical trials is challenging.

Quality-of-life assessment

Evidence of the effects of treatment on the quality of life of patients is increasingly required by decision makers for reimbursement in some countries—eg, in Germany—as a measure of the patient-related benefit of an intervention. However, the reliability and validity of most of the scales used for the assessment of quality of life in AD are poor.³⁴³ New instruments for refined, disease-specific quality-of-life assessment in AD, including early disease stages, are being validated and will increasingly be integrated into observational studies and clinical trials.^{344,345}

Post-mortem diagnosis of AD

Despite biomarker discoveries in the clinical diagnostics of AD and other neurodegenerative dementias, neuropathological confirmation is still needed for a definitive diagnosis, which necessitates a post-mortem examination to confirm the presence of extracellular A β deposits and intraneuronal aggregates of neurofibrillary tangles in brain tissue (figure 6) according to the NIA–Reagan Institute criteria.³⁴⁶ Unfortunately, in many European countries and the USA, the number of autopsies has decreased by at least half since the 1970s. This trend could mask diagnostic errors that reduce the power of research studies and thereby hamper progress. Moreover, reduced autopsy rates could lead to less reliable records of cause of death, which is of even greater concern in an ageing population with chronic disorders, in which multiple morbidities could make the cause of death uncertain. The low autopsy rate for neurodegenerative diseases is particularly alarming, because the reported cause of death from dementia in Sweden, for example, has quadrupled since 1987. In a study of 176 consecutive

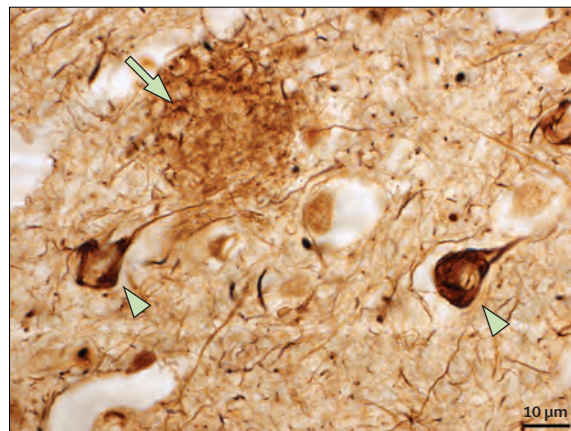


Figure 6: Neuropathological hallmarks of Alzheimer's disease

Post-mortem Bielschowsky silver staining of frontal cortex from a patient with Alzheimer's disease, showing the presence of a neuritic amyloid plaque (arrow), consisting of aggregated extracellular amyloid β fibrils, and intraneuronal neurofibrillary tangles (arrowheads), consisting of hyperphosphorylated tau protein. Neuritic plaques and neurofibrillary tangles are hallmarks of the disease, but more work is needed to understand the pathways that lead to pathology and the contributions of amyloid and tau pathology to neurodegeneration and the emergence of cognitive impairment and dementia.

neuropathological examinations of patients with clinically diagnosed dementia, the clinical and pathological diagnoses were in agreement in only 86 cases (49%).²³⁸ More standardised clinical and neuropathological diagnostic methods are under development.

Collaborative and specific efforts are needed to reverse the global decline in autopsy rates, with a particular focus on the neuropathological examination of patients included in clinical research studies or clinical trials. Indeed, advances in the neuropathological characterisation of neurodegenerative diseases suggest that a complex interplay of several pathologies underlies the clinical presentation of most common dementias, including AD,³⁴⁷ which has resulted in new guidelines for assessment.^{348,349} Of equal importance is the need for basic research studies on human brain tissue as a complement to in-vitro and in-vivo animal studies, which will be possible only if human brain and spinal cord tissue are collected after death.

Studies of other disorders suggest a correlation between autopsy rates and how strongly physicians recommend a post-mortem assessment.³⁵⁰ Thus, one strategy to increase autopsy rates is to train physicians and health-care professionals to understand and communicate the value of neuropathological confirmation of the diagnosis of AD and the need for researchers to have access to human post-mortem tissue for basic research. Another strategy is to build and facilitate national and international brain biobanking infrastructures to ensure that tissue is collected in line

with standardised and harmonised protocols, as achieved in the BrainNet Europe initiative.

Use of biomarkers in AD diagnosis

Biomarkers

The pathological hallmarks of AD—neuritic plaques composed of aggregated extracellular A β fibrils and intraneuronal neurofibrillary tangles of hyperphosphorylated tau (figure 6)—are associated with neurodegeneration and brain atrophy (section 5). Various methods can be used to monitor these brain changes as the disease progresses. Brain volume and structure can be investigated by computed tomography (CT) and magnetic resonance imaging (MRI). The size of particular (disease-relevant) brain regions, such as the temporal lobe (hippocampus), is used to assess brain atrophy in AD.³⁵¹ To study the functional activity of the brain, imaging techniques such as PET are used to measure cerebral brain glucose metabolism and cerebral blood flow, both of which correlate with cognitive function.³⁵² Molecular PET also allows detection of AD pathology manifested as amyloid plaque deposition.³⁵² Several PET tracers are under development for the imaging of tau deposition in AD and non-AD dementia disorders.³⁵³ CSF can easily be obtained by lumbar puncture, which is a well established and safe procedure in clinical neurology.³⁵⁴ A CSF test result that shows increased concentrations of total tau (T-tau) and phosphorylated tau (P-tau), and decreased concentrations of A β 42,³⁵⁵ suggests AD-like neurodegeneration in conjunction with A β pathology.

Several diagnostic biomarkers have been developed to detect AD neuropathology even in individuals at preclinical stages of the disease. Diagnostic biomarkers are markers of in-vivo pathology that are present at all stages of the disease, and they can therefore be used to detect AD pathological changes even in the asymptomatic state. PET of amyloid plaques in the brain and measurement of A β 42 and P-tau in the CSF are examples of diagnostic markers (figures 7, 8). By contrast, a progression marker, which might have poor disease specificity and might not be present at early stages, indicates clinical severity (ie, changes as the disease progresses). PET of cerebral glucose metabolism, measurement of T-tau in the CSF, and brain atrophy measured by MRI can be viewed as markers of disease progression (figure 9).³⁵⁶

Amyloid imaging and CSF biomarkers thus enable early detection of AD and, most importantly, discrimination of patients with mild cognitive impairment who have underlying AD pathology (prodromal AD) and are therefore at a high risk of progression to AD dementia (appendix).^{357,358} Three amyloid PET tracers—florbetapir (Amyvid; Eli Lilly, Indianapolis, IN, USA), florbetaben (Neuraceq; Piramal, Berlin, Germany), and flutemetamol (Vizamyl; GE Healthcare, Waukesha, WI, USA)—have been approved

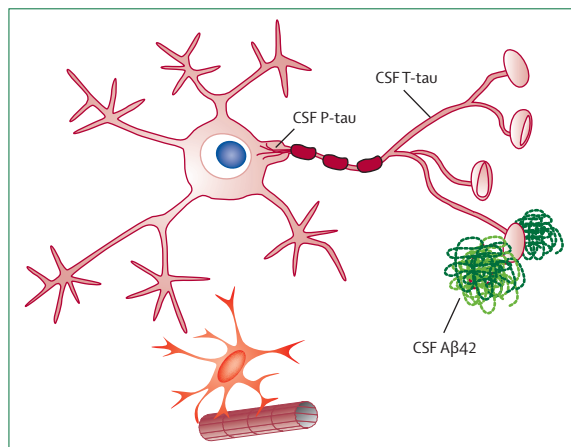


Figure 7: Pathological changes associated with cerebrospinal fluid biomarkers for Alzheimer's disease

Schematic representation of a neuron, showing the pathological changes associated with the three core CSF biomarkers of Alzheimer's disease. Increased CSF concentration of T-tau is a marker of axonal degeneration, increased CSF concentration of P-tau suggests the presence of neurofibrillary tangles, and decreased CSF concentration of the 42-aminoacid form of A β (A β 42) relates to senile plaque pathology. In future, newly discovered CSF, blood, or brain imaging (eg, MRI, PET) biomarkers could allow early diagnosis, including the subtyping of Alzheimer's disease, and personalised-medicine approaches to treatment and prevention. CSF=cerebrospinal fluid. T-tau=total tau. P-tau=phosphorylated tau. A β =amyloid β . MRI=magnetic resonance imaging. PET=positron emission tomography.

by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in the clinical assessment of memory disorders to exclude AD.³⁵⁹

The International Federation of Clinical Chemistry and Laboratory Medicine and the Global Biomarker Standardization Consortium are making progress to create certified reference methods and materials to standardise CSF biomarkers,^{360,361} and a fully automated assay of CSF A β 42 with very low inter-laboratory coefficients of variation (1–4%) was described in 2015.³⁶² Although structural imaging is well established in the clinical assessment of memory impairment, the use of CSF and PET biomarkers of tau and A β pathology are becoming part of the clinical routine in memory assessments at specialist clinics in Europe. However, in many countries, important questions remain about the reimbursement from health insurance for such procedures.

The use of these biomarkers in longitudinal studies of cognitively healthy individuals at risk of AD has shown that the pathophysiological process of AD begins a decade or more before the appearance of symptoms. A prospective cohort study³⁶³ suggested that A β deposition is slow and that it takes around 20 years before the onset of clinical symptoms. Meta-analyses show a correlation between amyloid positivity and clinical diagnosis, age, and APOE genotype.^{364,365} Because a patient with clinical symptoms of mild AD will already have a substantial loss of neurons in specific brain regions, such as the entorhinal cortex,³⁶⁶ the reversal or slowing down of symptomatic decline at this disease stage is extremely difficult. Disease-modifying approaches will probably work best in clinical trials that aim to prevent the progression of the clinical syndrome in individuals with very mild or no clinical symptoms, but with a genetic predisposition to AD or positive CSF or radiological AD biomarkers (ie, preclinical or prodromal AD).³³⁰

In trials already underway,³⁶⁷ biomarkers will be assessed before and after treatment initiation to ascertain whether any drug-related clinical benefit correlates with biomarker evidence of a change in the underlying disease process. By such an approach, the drug's effect on the target would be validated, and the validity of the biomarkers would be established, which would help in the design of new trials. Specifically, biomarkers could be used to establish whether negative trial results are a result of the absence of drug effects on the intended target, or whether the intended target changed in the expected direction but without any clinical benefit. Similarly, a finding of clinical benefit in a positive trial would be strengthened if it was backed by expected biomarker changes.

Proteomic studies of plasma biomarkers in AD have so far been disappointing, with only a few replicated positive results.³⁶⁸ A study of lipid profiles in the plasma of older adults (age ≥ 70 years) suggested that it might be possible to discriminate older adults with AD from cognitively healthy individuals by the use of a blood test,³⁶⁹ but independent

replication of these results is needed. Novel approaches, such as analysis of the profile of the different sugars (ie, glycans attached to proteins) in CSF or plasma might be helpful. Defects in the glycosylation of proteins involved in pathogenesis, such as tau, have been reported.³⁷⁰ The stratification of patients on biomarker grounds—eg, by amyloid and tau PET or by the use of CSF A β and tau markers to establish whether they have A β -predominant or tau-predominant disease—might become possible when methods for the PET imaging of tau deposition in the brain are available. Methods for the detection of other processes, such as neuroinflammation or cerebrovascular dysfunction, by MRI, PET, or CSF biomarkers might also be useful. The aim will be to personalise the selection of drugs for individual patients on objective grounds.

Finally, novel generic markers of neurodegeneration (eg, markers of synaptic dysfunction) that might be relevant to a broad range of neurodegenerative disorders would be helpful to assess the effects of disease-modifying treatments intended to slow down neurodegeneration. Novel ultrasensitive measurement techniques have just opened up the possibility of measuring such biomarkers in serum and plasma.³⁷¹

Clinical use of biomarkers

Biomarkers of Alzheimer's disease are in a transitional state between research and clinical practice. Widespread application to enable accurate, early, and differential

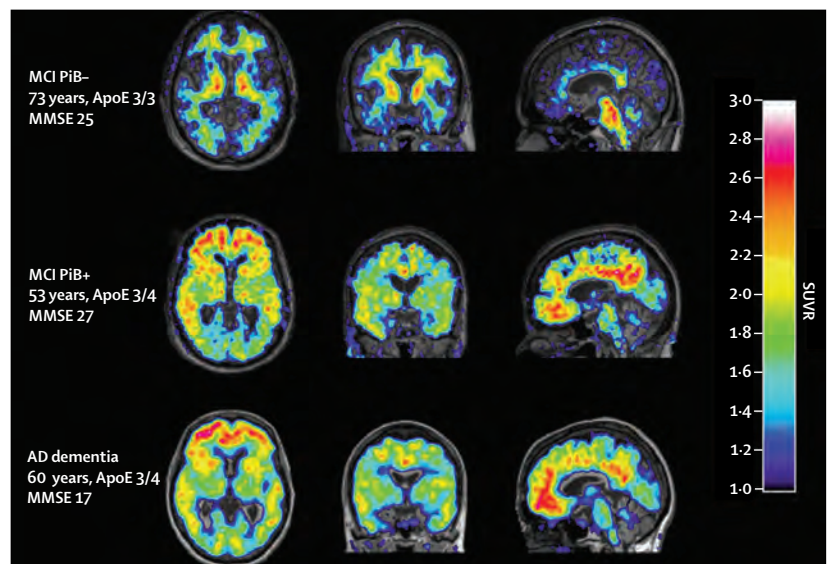


Figure 8: Deposition of fibrillar amyloid plaques in patients with mild cognitive impairment and Alzheimer's disease

Deposition of fibrillar amyloid plaques measured with PiB (a radioactive compound that binds to amyloid β peptide) PET in two patients with MCI and one patient with AD. Fusion images from coregistered PET and MRI scans are presented as transverse (left), coronal (middle), and sagittal (right) sections. The patients with MCI were clinically followed up for 2–5 years. The condition of the patient with MCI and low ^{11}C -PiB retention (PiB-) remained as MCI and did not convert to AD, whereas the patient with MCI and high ^{11}C -PiB retention (PiB+) converted within 2–5 years to AD dementia. Standard ^{11}C -PiB uptake values are expressed in relation to the cerebellum on a colour scale. Image courtesy of A Nordberg, Karolinska Institute, Huddinge, Sweden. PiB= ^{11}C -Pittsburgh compound B. PET=positron emission tomography. MCI=mild cognitive impairment. AD=Alzheimer's disease. MRI=magnetic resonance imaging. ApoE=apolipoprotein E. MMSE=Mini-Mental State Examination score. SUVR=standard uptake value cerebellum ratio.

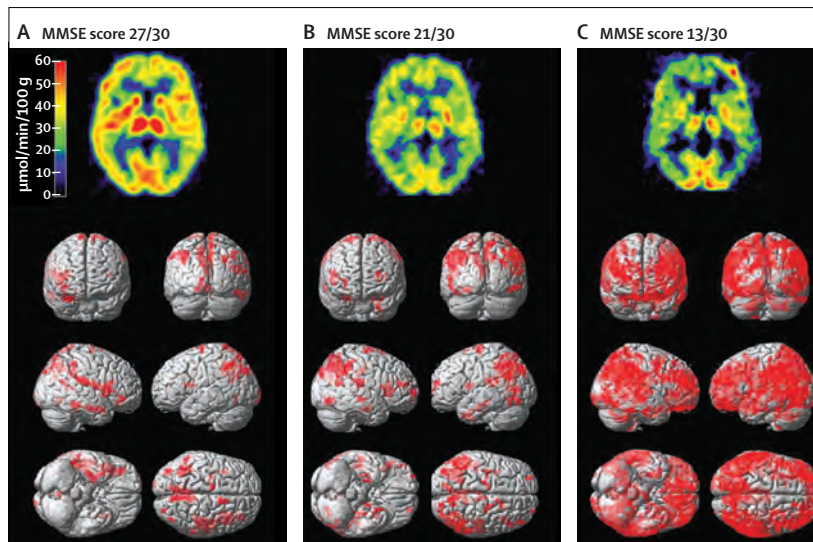


Figure 9: Progressive reduction in regional cerebral glucose metabolism in a patient with Alzheimer's disease
The upper row shows PET images of regional glucose metabolism ($\mu\text{mol}/\text{min}/100\text{ g}$), as measured by ^{18}F -FDG uptake, in a woman with a diagnosis of Alzheimer's disease at the age of 53 years (A), 56 years (B), and 58 years (C). ^{18}F -FDG uptake values are expressed on a colour scale (red indicates high uptake, yellow medium, and blue low). The lower row shows a three-dimensional rendering of the brain from the same patient (a representation of statistical parametric mapping of ^{18}F -FDG PET images), where red depicts areas in which regional cerebral glucose metabolism was significantly reduced during the progression of Alzheimer's disease compared with that in a group of healthy participants ($p=0.001$). Reproduced from Kadir and colleagues,³⁶⁶ by permission of Oxford University Press. PET=positron emission tomography. ^{18}F -FDG= ^{18}F -fluorodeoxyglucose. MMSE=Mini-Mental State Examination.

diagnosis of AD is being delayed by several methodological, economic, and political factors. Particularly, their practical usefulness is questioned in the absence of interventions to substantially delay the progression of neurodegeneration. The main methodological factor is related to standardisation. The economic and political factors relate to costs of sample acquisition and analysis, and how biomarker results affect the clinical management of patients.

Many AD biomarkers are not sufficiently standardised to be applied routinely in clinical practice, but standardisation initiatives are underway.^{360,372,373} Europe is not homogeneous in terms of technology (eg, neuroimaging scanners and laboratory equipment) and personnel with the necessary expertise; diagnosis of neurodegenerative diseases in memory clinics is, at present, made largely on clinical grounds, with brain imaging (CT or MRI) and clinical chemistry tests (CSF tau and A β) to exclude other potential causes of cognitive decline, such as depression, normal pressure hydrocephalus, or cerebrovascular changes. Recently proposed diagnostic algorithms that incorporate AD biomarkers—the NIA-AA^{325–327} and IWG^{328–330} research diagnostic criteria (table 8)—are being adapted to clinical realities across Europe. For example, the EU JPNB Biomarkers for Alzheimer's Disease and Parkinson's Disease (BIOMARKAPD) project is a pan-European network of memory clinics and laboratories engaged in the uniform implementation and standardisation of

diagnostic algorithms in the assessment of patients who seek medical advice because of cognitive symptoms.

The development and standardisation of biomarkers as practical and affordable tools for clinical use will be essential to prepare for the next generation of preventive and disease-modifying AD drugs. The diagnostic use of biomarkers will be given a substantial boost by the availability of treatments proven to be effective at the pre-dementia stages of AD. If the ongoing secondary prevention trials with anti-amyloid therapies are successful (section 7), patients could be selected for treatment during the preclinical stages of AD on the basis of biomarker detection.³⁶⁷ Treatment should be initiated at specialist clinics until more information about the clinical use of such therapies has been obtained. From a safety and cost perspective, exclusion of individuals from some treatments will also be important—eg, an amyloid-negative patient should not be treated with an anti-amyloid drug.

Summary and recommendations

Diagnosis of AD and other dementias is complex, requiring cognitive and functional assessment, sometimes with serial evaluations, and exclusion of other morbidities that can cause dementia. New, robust, and affordable methods are needed for the diagnosis of AD, especially at early (pre-dementia) stages. The use of biomarkers—from blood, CSF, and brain imaging such as MRI or PET—is not yet widespread, except in the setting of clinical trials in specialist clinics. Better approaches are needed for subjective cognitive testing, in addition to validated objective diagnostic criteria for AD. We make the following recommendations for much-needed improvements in diagnosis.

(1) At a time when no effective treatment exists, an accurate appraisal of the value of diagnosis for society and for the care of individual patients is needed if decision makers are to allocate public funds to relatively expensive diagnostic procedures. Virtually no studies of this aspect of diagnosis have been done so far.

(2) Methods are needed to measure the cognitive characteristics of prodromal AD. New methods should be sensitive to minor impairment and subtle changes, and should be robust in application and informative in the populations for whom they are intended. Knowledge of the cognitive components of AD at very early disease stages could be used to predict cognitive and functional decline, to assess the effectiveness of interventions, and for stratification of patients in clinical trials.

(3) Biomarkers need to be further developed into standardised and affordable tools that can be used routinely in clinical practice to select patients for appropriate care and treatment. The diagnostic use of biomarkers will increase as treatments proven to be effective at the pre-dementia stages of AD become available.

(4) Some biomarkers are already being used in memory clinics. However, guidelines are needed for the routine

application of biomarkers in the diagnosis of AD to avoid uncontrolled, poor, or non-cost-effective use. Overuse could lead to the identification of AD-related pathological changes with uncertain relevance to the symptoms presented; underuse could lead to the misdiagnosis of AD as depression or other non-degenerative brain disorders.

(5) Data are needed on the added diagnostic value of individual biomarkers and the cost-effectiveness of different sequences of biomarker assessment, in addition to a detailed characterisation of patients in whom biomarkers are assessed, including age, comorbidities, and social factors (eg, education level).³⁷⁴

(6) The search for novel biomarkers with higher predictive value at pre-dementia stages of the disease should be continued, and simple, low-cost assays (preferably in blood) that could be used in general practice should be developed.

Section 7. Pharmacological treatment of Alzheimer's disease

The increasing number of people with AD is leading to substantially more use of pharmacological treatments and greater medication costs. For example, in Sweden, the total drug costs for people with dementia constituted about 1.1% of the societal costs of dementia in 2000, 1.6% in 2005, and 1.8% in 2012.³⁷⁵ Although drug costs are a small proportion of the total societal cost of dementia (the largest proportion of costs, around 80%, is within the municipal sector, for long-term care), they constitute a noteworthy proportion of health-care costs for people with dementia. In Sweden, the cost of dementia drugs as a proportion of the costs of dementia care in the health sector increased from 23% in 2000, to 39% in 2012.³⁷⁵ This trend indicates that the incentives to provide treatment from the perspective of health-care budgets might differ from a societal viewpoint, because the economic impact of dementia drug costs on the health sector is so large. Moreover, the drift in diagnostic boundaries of AD towards earlier diagnosis might lead to greater use of marketed drugs even in the absence of efficacy evidence in pre-dementia cognitive impairment.

Marketed drugs for Alzheimer's disease

Approved drugs marketed in Europe are the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine. They are indicated for mild-to-severe AD or moderately-severe-to-severe AD, respectively. All are approved for the dementia of AD, and rivastigmine is approved for Parkinson's disease dementia. In Europe, no drugs are approved for preclinical AD, prodromal AD, or mild cognitive impairment, or for at-risk conditions (prevention). In the USA, however, these drugs are provided for patients at pre-dementia stages.

As all approved drugs are now available as generics, the price has dropped substantially. For example, the price of donepezil has fallen by 98% in Sweden, by 97% in the

UK, and by 84% in Germany, similar to previous price drops for drugs such as enalapril, simvastatin, and citalopram. However, although total prescriptions have risen because of the increasing number of people with AD, prescription rates have not necessarily increased, perhaps because information campaigns from drug companies have decreased or because the known and approved target population has already been reached. Proprietary formulations of donepezil 23 mg, memantine 28 mg, and higher-dose rivastigmine patch (transdermal formulation) are being marketed in Europe to compete with the generics, despite the absence of evidence that higher doses of proprietary drugs are more effective than the lower recommended doses.

Effectiveness of marketed drugs

The evidence we present comes from clinical and efficacy studies of marketed drugs for the treatment of AD, and does not address other disorders, such as cognitive impairment due to mixed AD, dementia with Lewy bodies, or ageing in the oldest old. Although AD influences many functional domains, the main focus of, and primary outcome in, most AD trials has been cognitive function. Other potential meaningful outcomes, such as global measures of functionality, ADL, and behaviour, are in most studies secondary outcomes, and are more relevant in advanced dementia than in early phases of the disease. Studies in mild AD cases should include outcomes that focus on memory functions, whereas in later stages of the disease, effects on ADL and psychiatric and behavioural disturbances are more clinically relevant.

Efficacy based on cognitive tests and inventories of daily activities can be assessed reliably in clinical trials of drugs for AD. However, the effects of the marketed acetylcholinesterase inhibitors have been statistically small, and just how effective, and cost effective, they are remains controversial. The few RCTs in which data for resource use and costs have been collected have not shown any significant cost savings or cost-effectiveness for the brand-name drugs.³⁷⁶ However, these clinical trials have not been designed for economic evaluations and their duration has been short (6–12 months) in relation to the period over which long-term cost-effectiveness is of interest. Thus, several simulation approaches have been used, in which inputs of effectiveness and data for mortality and costs can be applied to, for example, the expected period of survival.³⁷⁷ The conclusion from such simulations (largely sponsored by drug companies) is that treatment is cost effective.^{376,378} Notably, these models assume long-term use of the drugs over several years, even though most patients take them in the shorter term.

Outcomes from trials of approved drugs cannot easily be generalised to clinical practice or to effectiveness. Study populations in RCTs are generally highly selected in terms of inclusion and exclusion criteria. Very old people (eg, age ≥ 85 years), who constitute a great proportion of the population with AD, and people with

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medical comorbidities (which are common in the oldest old) are underrepresented, making generalisations from trials to the clinical practice of dementia care problematic. Duration of treatment in clinical trials is generally up to 6 months, with only a few trials extending beyond this period. In clinical trials, acetylcholinesterase inhibitors can be tapered and withdrawn without loss of function over 8 weeks; there is no need to substitute memantine. Most patients can be withdrawn from treatment when uncertainty exists about its effects.³⁷⁹ Little unbiased information exists on long-term use or safety. Rather, there is a reliance on medical records from research centres, research cohorts, and prescribing data.

Long-term effective therapy for cognitive impairment is a major unmet need. A drug that provides even 1–2 years of stable function or quality of life would be useful and cost effective,³⁸⁰ irrespective of whether the underlying pathology of AD is affected. Indeed, clinical trials of drugs in development for prodromal AD and mild AD dementia are 18–24 months in duration to show longer-term effects.

For policy makers and stakeholders, long-term cost-effectiveness might be of greater interest than efficacy in trials or clinical effectiveness. Since such long-term data are unlikely to be available from clinical trials, other sources such as economic simulations, registry data, or results from epidemiological studies might be of interest.

	Donepezil		Rivastigmine		Galantamine		Memantine	
	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement
Austria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bulgaria	Yes	No	Yes	No	Yes	No	No	No
Croatia	Yes	No	Yes	No	No	No	Yes	Yes
Cyprus	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Czech Republic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Denmark	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Estonia	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Finland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Germany	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Greece	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hungary	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Iceland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ireland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Italy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jersey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Latvia	Yes	No	Yes	No	Yes	No	Yes	No
Lithuania	Yes	Yes	No	No	No	No	Yes	Yes
Luxembourg	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Malta	Yes	No	Yes	No	Yes	No	Yes	No
Netherlands	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Norway	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poland	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Portugal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Romania	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Slovakia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Slovenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sweden	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Switzerland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Approval and reimbursement in European countries for drugs with European Medicines Agency approval for marketing for Alzheimer's disease: the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine (indicated for mild-to-severe Alzheimer's disease) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (indicated for moderately-severe-to-severe Alzheimer's disease). Information obtained from Alzheimer Europe.³⁸⁰

Table 9: Approval and reimbursement for drugs on the market for Alzheimer's disease in Europe

These alternative sources have lower credibility than RCTs in terms of quality of evidence. Thus, no single design can be used to judge effectiveness, and a synthesised approach in which results from several sources are used might be a feasible way forward. Furthermore, instead of focusing on single drugs, combined drug treatment (and the combination of drug treatment with various non-pharmacological options) in various settings is perhaps the best approach. The total effect of an intervention package is of primary importance, rather the effects of single interventions, as shown in the FINGER study.¹⁸⁹

Effectiveness of drugs for disruptive behaviours

RCT evidence does not show donepezil or memantine to be effective for patients with significant behavioural disruption (ie, agitation or aggression).^{381,382} In patients with mild-to-moderate AD, measurable changes in response to these drugs can be measured on behaviour rating scales, but such patients do not have marked agitation, and the significance of the small mean change is unclear.³⁸³

Effective pharmacological treatment of behavioural symptoms is a challenge. Modest advantages of antipsychotics for delusions or aggression are offset by their considerable toxicity, and they should be used cautiously or avoided.³⁸⁴ Antidepressants have not been shown to be effective for depression in AD, but in some cases are modestly efficacious for behavioural symptoms (eg, citalopram for agitation in dementia).³⁸⁵ However, cardiovascular adverse effects and worsening cognition restrict their use as well.³⁸⁶ Anticonvulsants should not be used. Newer drugs with different mechanisms of action might eventually be helpful. The combination of non-pharmacological and pharmacological treatment is important—the total effect is of primary interest, not the effect of a single treatment component per se.³⁸⁷

Inequalities in treatment in Europe

Reimbursement is crucial to the availability of many drugs. Substantial inequalities exist in AD treatment across Europe, despite the presence of common standardised diagnostic and treatment procedures. The proportions of people with AD who receive treatment with approved drugs and treatment durations vary across Europe¹⁹ (table 9) and globally.³⁸⁹ These differences can be explained partly by variations in prescribing practices and reimbursement policies among European countries. In some countries, reimbursement requires decisions to be made by specialist doctors or in specialist centres; in other countries a continuous evaluation by a specialist of the treatment decision is also necessary (table 10). Reimbursement might not be made available to people with AD living alone or in nursing homes. Other systems require specific examinations before a reimbursement decision is made. Finally, substantial differences exist between European countries in the specified cognitive test scores that guide the initiation and discontinuation

of treatment. Although the situation varies across Europe, the drugs are both approved and reimbursed in most countries (table 9).

The centralisation of the market authorisation process at the level of the EMA has solved the problem of delays among European countries for the marketing of drugs for neurodegenerative disorders. However, the launch dates of products continue to vary across countries, as

	Initial prescription by specialists	Initial prescription by GPs	Continued treatment decisions by specialists	Continued treatment decisions by GPs
Austria	Yes	No	Yes	Yes (for 6 months)
Belgium	Yes	No	Yes	No
Bulgaria
Croatia	Yes*	No	Yes*	Yes*
Cyprus	..	Yes
Czech Republic	Yes	No	Yes	No
Denmark	Yes	No	Yes	Yes
Estonia
Finland	Yes	Yes†	Yes	Yes†
France	Yes	No	Yes	Yes
Germany	Yes	Yes	Yes	Yes
Greece	Yes	No	Yes	Yes
Hungary	Yes	No	Yes	No
Iceland
Ireland	Yes	Yes	Yes	Yes
Italy	Yes	No	Yes	No
Jersey
Latvia
Lithuania
Luxembourg	Yes	Yes	Yes	Yes
Malta	Yes	Yes	Yes	Yes
Netherlands	Yes‡	No	Yes‡	Yes‡
Norway	Yes§	Yes§	Yes§	Yes§
Poland	Yes	Yes	Yes	Yes
Portugal	Yes	No	Yes	No
Romania	Yes	No	Yes	No
Slovakia	Yes	No	Yes	No
Slovenia	Yes	No	Yes	Yes
Spain	Yes	No	Yes	No
Sweden	Yes	Yes	Yes	Yes
Switzerland	Yes	Yes	Yes	Yes
Turkey	Yes	No	Yes	Yes
UK	Yes	No	Yes	Yes

Prescription regulations for drugs approved for marketing in European countries: the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine (indicated for mild-to-severe Alzheimer's disease) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (indicated for moderately-severe-to-severe Alzheimer's disease). GP=general practitioner. *Memantine only. †Support with statement from specialist. ‡Not donepezil. §Restrictions for donepezil. Information obtained from Alzheimer Europe.³⁸⁸

Table 10: Prescription regulations of drugs on the market for Alzheimer's disease in Europe

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	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
Pioglitazone	PPAR γ agonist that acts as a β -secretase inhibitor; inhibits first protease needed for A β production	TOMMORROW (NCT01931566; phase 3)	3500 people aged 65–83 years with healthy cognition at risk of developing MCI due to AD, with risk stratification including age and TOMM40 and APOE genotype; a masked extension is planned with the aim of recruiting 316 participants who complete TOMMORROW with a diagnosis of MCI due to AD (NCT02284906; phase 3)	5 years (completion by 2019); extension study 2 years (completion in 2021)
Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	A4 study (NCT02008357; phase 3)	1150 people aged 65–85 years with healthy cognition, 500 of whom show evidence of brain amyloid accumulation	3 years plus 2 years' follow-up (completion by 2020)
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (<i>APP</i> , <i>PSEN1</i> , <i>PSEN2</i>)	2 years plus 3 years' follow-up (completion by 2019)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (<i>APP</i> , <i>PSEN1</i> , <i>PSEN2</i>)	2 years plus 3 years' follow-up (completion by 2019)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	API—autosomal dominant AD (NCT01998841; phase 2)	300 members of Colombian families with early-onset familial AD (age 30–60 years), including 200 carriers of an autosomal dominant AD-causing mutation in <i>PSEN1</i>	3 years plus 2 years' follow-up (completion by 2020)

Only selected phase 2 or 3 RCTs due for completion after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. PPAR γ =peroxisome proliferator-activated receptor γ . A β =amyloid β . MCI=mild cognitive impairment. AD=Alzheimer's disease. A4 study=Anti-Amyloid Treatment in Asymptomatic Alzheimer's study. DIAN-TU=Dominantly Inherited Alzheimer Network Trial Unit. API=Alzheimer's Prevention Initiative.

Table 11: Drugs in late-stage clinical development for Alzheimer's disease in people at risk of developing the disorder

do the timings for integration of approved drugs in the reimbursement system. Thus, inequalities in access to new drugs still exist. As the demand for social and medical care increases, successful medications that are priced fairly need to be introduced such that access to them is fair and equitable. Any effective treatment anticipated for people with pre-symptomatic, preclinical, or prodromal AD will increase the size of the market, and the numbers of patients should be estimated and provided for. Discussions are ongoing between the EMA and the FDA to harmonise the rules for drug approvals, because drug trials for approval are often done separately in the USA and Europe. A harmonised approach would be desirable because fewer trials would be required for approval across the USA and Europe.

Challenges and priorities

Several issues need to be considered with regard to the pharmacological treatment of AD at present: the diagnosis of AD, the selection of patients to be offered treatment (eg, which groups are likely to benefit), the use of evidence-based prescribing standards and patient-preference-based standards to assist in treatment decisions, and the need for reimbursements across health-care systems that are fair to patients and valid, including decisions to start and stop treatment and more consistent access and reimbursement policy across Europe. Patient-centred and family-centred standards for pharmacological treatment have yet to be developed. The use of current drugs needs to be linked to their ability to show better health outcomes, including better function. Continuing assessments of effectiveness are needed, including of the circumstances under which marketed

drugs are most helpful, and whether groups or individual patients can be recognised who might benefit from particular approaches.

Drugs in late-stage development

AD is a complex disease and several drug targets are under investigation. The amyloid cascade hypothesis has dominated the specialty for the past two decades, with an emphasis on A β pathways, but tau and small molecules are also the focus of investigation (section 5). The targets for AD are not yet validated and are potentially numerous, so alternatives to A β -targeting and tau-targeting drugs might be important in the future. Tables 11–13 list drugs that are in late-stage clinical development (phase 2–4), including mechanisms of action. The diagnostic targets for new drugs include at-risk populations (prevention) and preclinical or pre-symptomatic AD (table 11),^{326,330} prodromal AD³³⁰ (ie, mild cognitive impairment due to AD;³²⁵ table 12), or mild-to-moderate AD (table 13).³⁹⁰

Drugs that target A β

The most active research is taking place in the disruption of the amyloid pathway, because changes in A β production or clearance are thought to be among the earliest pathological changes and to lead to neurodegeneration in AD. New drugs include vaccines and antibodies to A β , and inhibitors and modulators of β -secretase and γ -secretase (section 5). The first vaccine to be tested in patients removed amyloid plaques, but caused brain toxicity and had no clinically significant benefits.^{391,392} Active trials of A β immunotherapies, which aim to increase the clearance of amyloid, are taking place with the monoclonal anti-amyloid antibodies solanezumab (Eli Lilly), gantenerumab

For more on drugs in development see <http://www.alzforum.org/therapeutics>

(Hoffmann-LaRoche), crenezumab (Genentech), and aducanumab (Biogen) (tables 11, 12), and with several A β vaccines, including CAD106 (Novartis; NCT02565511) and ACC-001 (Janssen, Pfizer; NCT01284387).

γ -secretase cleaves the precursor protein APP intracellularly to produce A β fragments, which are thought to be toxic and crucial to the pathogenesis of AD. This enzyme was regarded as a valid therapeutic target, but clinical trials of γ -secretase inhibitors (avagacestat³⁹³ and semagacestat³⁹⁴) failed, with an unexpected degree of toxicity and worsening of cognition, possibly because of off-target effects, the particular drugs used, or dosing.³⁹⁵

β -secretase, including the form known as BACE1, cleaves APP extracellularly to produce A β peptides. The development of BACE1 inhibitors is being avidly pursued and several have entered clinical trials in people with prodromal AD or AD dementia, including E2609 (Eisai; tables 12, 13), AZD3293 (AstraZeneca; tables 12, 13), HPP854 (High Point Pharmaceuticals; NCT01482013), and LY3202626 (Eli Lilly; NCT02323334); others are in preclinical stages of development. The most advanced is verubecestat (MK-8931; Merck), which is in combination phase 2/3 trials for either prodromal AD (table 12) or

mild-to-moderate AD dementia (table 13). In phase 1, it reduced CSF concentrations of total and soluble A β by up to 84% and 88%, respectively. The phase 2/3 trials (NCT01739348 and NCT01953601) will include about 1800 participants, each treated over 18–24 months. Outcomes and marketing authorisation (if successful) are expected in 2018.

Drugs that target tau

Although the mechanistic link between A β deposition and tau pathology—and their contributions to neurodegeneration and the clinical manifestations of AD—remain unclear, treatment approaches that aim to downregulate tau-related toxicity might be of clinical benefit. Drugs that reduce the pathological hyperphosphorylation of tau protein, or the fibrillation or deposition of tau, are in development (section 5). These effects have been shown in vitro for several drugs, often inhibitors of GSK3 β ,^{280,281} a kinase involved in the generation of hyperphosphorylated tau. Several companies have been developing similar tau-related approaches, including AbbVie, Bristol-Myers Squibb, Lundbeck, Pfizer, and TauRx Therapeutics.

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for A β production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for A β production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for A β production	APECS (NCT01953601; phase 3)	1500 people aged 50–85 years with prodromal AD	2 years (completion in 2018)
JNJ-54861911	BACE1 inhibitor: inhibits first protease needed for A β production	NCT02260674 (phase 2)	100 people aged 50–85 years with early (pre-dementia) AD; an extension study of 100 people with early AD (50–85 years) who participated in previous phase 1 and phase 2 RCTs with the drug is ongoing (NCT02406027; phase 2)	10 months (completion in 2016); extension study 2 years (completion in 2024)
Reduced aggregation or oligomerisation of amyloid				
PQ912	Glutamyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified A β peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01224106 (phase 3)	799 people aged 50–85 years with prodromal AD	2 years (completion in 2015)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIB037)	Anti-amyloid monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	2700 people (1350 per trial) aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Intravenous immunoglobulin derived from healthy donors	Passive immunotherapy (contains naturally occurring polyclonal anti-A β antibodies)	NCT01300728 (phase 2)	50 people aged 50–84 years with MCI	2 years (completion in 2017)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged \geq 60 years with MCI or mild AD dementia	About 18 months (completion in 2016)

(Table 12 continues on next page)

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Mechanism	RCTs	Participants	Duration	
(Continued from previous page)				
Modulation of neurotransmission				
Atomoxetine	Noradrenaline reuptake inhibitor (licensed): increases brain concentrations of noradrenaline	ATX-001 (NCT01522404; phase 2)	40 people aged 50–90 years with MCI	6 months (completion in 2017)
Ladostigil (TV-3326)	Acetylcholinesterase inhibitor and MAO inhibitor: increases cholinergic neurotransmission and transmission mediated by monoamines; a derivative of rasagiline and rivastigmine, it also has antioxidant properties and can modulate APP processing and cellular signalling pathways	NCT01429623 (phase 2)	200 people aged 55–85 years with MCI	3 years (completion in 2015/2016)
DAOIB	NMDA receptor regulator: enhances NMDA-receptor-mediated glutamatergic neurotransmission	NCT02239003 (phase 2)	50 people aged 50–90 years with MCI	6 months (completion in 2016)
PXT00864*	Regulates GABAergic neurotransmission (depending on the receptor, it can have antagonistic or agonistic effects)	PLEODIAL-I (NCT02361424; phase 2)	45 people aged ≥60 years with mild AD dementia; an open-label extension study, PLEODIAL-II, is ongoing (NCT02361242; phase 2)	12 weeks (completion in 2015); extension study 24 weeks
Other mechanisms of action				
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can reduce amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
Cilostazol	PDE3 inhibitor (licensed antiplatelet drug): can reduce amyloid toxicity	COMCID (NCT02491268; phase 2)	200 people aged 55–84 years with MCI	About 2 years (completion in 2018)
BI 409306 (SUB 166499)	PDE9 inhibitor: enhances synaptic plasticity and reduces amyloid toxicity	NCT02240693 (phase 2) and NCT02337907 (phase 2)	624 people aged ≥55 years with MCI due to AD	12 weeks (completion in 2016)
Simvastatin	Cholesterol-lowering drug (licensed) with antioxidant and anti-inflammatory properties: can lower brain Aβ production and reduce Aβ-mediated neurotoxicity	SIMaMCI (NCT00842920; phase 4)	520 people aged 55–90 years with amnesic MCI	2 years (completion in 2018)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)
Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. APECS=β Amyloid Production and Effects on Cognition Study. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. MAO=monoamine oxidase. APP=amyloid precursor protein. NMDA=N-methyl-D-aspartate. GABA=γ-aminobutyric acid. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. PDE=phosphodiesterase. SIMaMCI=Simvastatin in Amnesic Mild Cognitive Impairment. *A combination of acamprosate and baclofen (both licensed drugs).				
Table 12: Drugs in late-stage clinical development for Alzheimer's disease in people at symptomatic, pre-dementia stages				

Among other targets³⁹⁶ is the dynamic O-linked N-acetylglucosamine (O-GlcNAc) post-translational modification of tau, which might relate to tau hyperphosphorylation. Concentrations of O-GlcNAc are decreased in the brains of patients with AD. Merck and Alectos Therapeutics have collaborated to inhibit the enzyme involved in removal of O-GlcNAc sugars, with some preclinical evidence that this approach can slow neurodegeneration and reduce tau and amyloid pathology.^{397,398} Antibodies can target the MAPT gene or tau protein, and several approaches are in development.^{282,288,396} For example, in January 2015, AC Immune partnered with Johnson & Johnson to develop the liposome-based anti-tau vaccine ACI-35.³⁹⁹ A phase 1 study of active vaccination against tau with AADvac1 (Axon Neuroscience; NCT01850238 and NCT02031198) is also in progress. Another drug that is being developed with the aim of increasing tau clearance—on the basis of the view that tau clearance in general must be achieved to modify disease progression—is methylene

blue, an FDA-approved compound that can inhibit tau aggregation. A formulation of methylene blue, TRx0237 (LMTX; TauRx Therapeutics; table 13), is being tested in a phase 3 trial of 833 patients with mild-to-moderate AD, with patients followed up for 12 months (NCT01689246), and a phase 2 trial of 500 patients with mild frontotemporal dementia, followed up for 18 months (NCT01626378). Outcomes of both trials are expected in 2016. Other drugs in late-stage clinical development for prodromal AD or AD dementia include exenatide (tables 12, 13) and liraglutide (table 13).

The way forward in therapeutic development

Since the advent of the acetylcholinesterase inhibitors, drug development for AD has been disappointing. All drugs in completed phase 2 and phase 3 trials have failed. Pursuit of the amyloid cascade hypothesis has not so far been rewarding, and clinical research efforts are now being directed more broadly. Drug development is moving towards earlier stages of the disease, with RCTs

in people with preclinical and prodromal AD. This approach raises important questions about the future of drug development for AD, including the issues of ethics, cost sustainability of new treatments, validity and costs of diagnostics (biomarkers) and analyses, and durations of trial participation for people with AD and their families. To accelerate the process of drug development, new trial designs are needed, with expedited programmes for the

testing and approval of drugs to address the unmet needs of patients. Moreover, improvements in basic and translational research are needed for the discovery of new targets and new drugs for clinical development.

The shift to earlier stages of AD

In future, if drugs are approved for AD and marketed as disease modifying or as long-term treatments, diagnostic

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for A β production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for A β production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for A β production	EPOCH (NCT01739348; phase 2/3)	1960 people aged 55–85 years with mild-to-moderate dementia due to AD	18 months (completion in 2017) with 5 year double-blind extension phase
Bryostatin-1	Macrocyclic lactone (has been investigated as an antineoplastic drug): stimulates α -secretase and reduces brain amyloid burden	NCT02431468 (phase 2)	150 people aged 55–85 years with moderate-to-severe dementia due to AD	7 months (completion in 2017)
Reduced aggregation or oligomerisation of amyloid				
Carvedilol	Non-selective β -adrenoceptor blocker (approved for congestive heart failure and hypertension): prevents formation of amyloid oligomers	NCT01354444 (phase 4)	50 people with mild dementia due to AD*	6 months (completion in 2016)
PQ912	Glutamyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified A β peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	EXPEDITION 3 (NCT01900665; phase 3)	2100 people with mild AD dementia; an open-label extension study, EXPEDITION EXT, is underway to assess safety in 1275 people with dementia due to AD (≥ 55 years) who previously participated in phase 3 RCTs with solanezumab (NCT01127633; phase 3)	18 months (completion in 2018); extension study 2 years (completion in 2018)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT02051608 (phase 3)	1000 people aged 50–90 years with mild AD dementia	About 2 years (completion in 2018)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid human monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	1700 people aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01723826 (phase 2)	A long-term, open-label safety extension study in 360 people with mild-to-moderate dementia due to AD who previously participated in phase 2 RCTs of the antibody	About 2 years (completion in 2017)
Albumin and immunoglobulin associated with plasmapheresis	Passive immunotherapy	AMBAR (NCT01561053; phase 2/3)	350 people aged 55–85 years with mild-to-moderate AD dementia	14 months (completion in 2016)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
TRx0237	Tau aggregation inhibitor: reduces abnormal tau accumulation	NCT01689246 (phase 3) and NCT01689233 (phase 3)	About 1533 people aged <90 years with mild-to-moderate AD dementia	About 18 months (completion in 2016)
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥ 60 years with MCI or mild AD dementia	About 18 months (completion in 2016)
Liraglutide	GLP1 receptor agonist (approved diabetes drug): improves insulin brain signalling and can prevent tau hyperphosphorylation	ELAD (NCT01843075; phase 2)	206 people aged 50–85 years with mild dementia due to AD	12 months (completion in 2017)

(Table 13 continues on next page)

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Mechanism		RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Donepezil	Acetylcholinesterase inhibitor (already approved for dementia due to AD): increases brain levels of acetylcholine	NCT01129596 (phase 4), NCT01251718 (phase 4), and NCT02162251 (phase 4)	Post-marketing surveillance studies of 1600 people with mild-to-severe AD dementia*	Up to 4 years (completion in 2015/2016)
Encenicline (MT-4666, EVP-6124)	$\alpha 7$ nicotinic acetylcholine receptor agonist (increases cholinergic neurotransmission)	NCT02246075 (phase 2), NCT02327182 (phase 3), NCT01969136 (phase 3), and NCT01969123 (phase 3)	1930 people aged 50–85 years with mild-to-moderate AD dementia; an extension study is planned with the aim of recruiting 1000 participants from these studies (NCT02004392; phase 3)	6–12 months (completion in 2016/2017); extension study 6 months (completion in 2017)
MK-7622	Allosteric modulator of muscarinic acetylcholine receptors (postulated): enhances response to acetylcholinesterase inhibitors, increasing cholinergic neurotransmission	NCT01852110 (phase 2)	830 people aged 55–85 years with mild-to-moderate dementia due to AD	Up to 1 year (completion in 2020)
Rasagiline	MAOB inhibitor (licensed for Parkinson's disease): increases neurotransmission mediated by monoamines	R2 (NCT02359552; phase 2)	50 people aged 50–90 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
RG1577 (RO4602522)	MAOB inhibitor: increases neurotransmission mediated by monoamines	NCT01677754 (phase 2)	544 people aged 50–90 years with moderate AD dementia	1 year (completion in 2015)
Idalopirdine (Lu AE58054, SGS 518)	5-HT ₂ receptor antagonist: can enhance cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission	STARSHINE (NCT01955161; phase 3), STARBEAM (NCT02006641; phase 3), and STARBRIGHT (NCT02006654; phase 3)	2490 people aged ≥ 50 years with mild-to-moderate AD; an extension study, STAR Extension, with 1770 people from STARSHINE AND STARBEAM is ongoing (NCT02079246; phase 3)	6 months; extension study 8 months (completion in 2015/2016)
Riluzole	Decreases glutamatergic neurotransmission by inhibiting both glutamate release and postsynaptic glutamate receptor signalling	NCT01703117 (phase 2)	48 people aged 60–85 years with mild dementia due to AD	6 months (completion in 2017)
DAOIB	NMDA receptor regulator: enhances NMDA receptor-mediated glutamatergic neurotransmission	NCT02103673 (phase 2)	90 people aged ≥ 50 years with AD or vascular dementia at stages from mild to moderate-severe	6 weeks (completion in 2016)
Methylphenidate	Dopamine and noradrenaline reuptake inhibitor (licensed): acts as a stimulant by promoting dopaminergic and noradrenergic neurotransmission	ADMET2 (NCT02346201; phase 3)	200 people with mild-to-moderate AD dementia and apathy	6 months (completion in 2019)
Other mechanisms of action				
Sagramostim	Licensed synthetic form of the haemopoietic growth factor GM-CSF: promotes amyloid removal by stimulating phagocytosis	NCT01409915 (phase 2)	40 people aged 55–85 years with mild-to-moderate AD dementia	6 months (completion in 2016)
Formoterol	Longacting β_2 -adrenoceptor agonist (approved for asthma and chronic obstructive pulmonary disease): can improve synaptic plasticity and reduce amyloid burden	NCT02500784 (phase 2)	60 people aged 50–85 years with mild-to-moderate dementia due to AD	1 year (completion in 2016)
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥ 65 years with MCI or mild AD dementia	1 year (completion in 2018)
ATP (small molecule)	Enhances metabolism and can protect against amyloid-mediated cytotoxicity	NCT02279511 (phase 2)	20 people aged 55–85 years with moderate-to-severe AD dementia	3 months (completion in 2016)
Azeliragon (PF-04494700, TTP488; small molecule)	RAGE inhibitor: can counteract brain amyloid accumulation and modulate inflammation	NCT02080364 (phase 3)	800 people aged ≥ 50 years with mild AD dementia	18 months (completion in 2018)
T-817MA (small molecule)	Has neurotrophic and neuroprotective properties: can protect against amyloid-mediated and tau-mediated toxicity	NCT02079909 (phase 2)	450 people aged 55–85 years with mild-to-moderate AD dementia	About 1 year (completion in 2016)
Cerebrolysin†	Peptide mixture with neurotrophic-like properties related to regulation of cell signalling: can control amyloid metabolism and has anti-apoptotic effects mediated by expression of endogenous neurotrophic factors	NCT01822951 (phase 4)	510 people aged ≥ 50 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
Nilvadipine	Dihydropyridine calcium channel blocker (licensed antihypertensive): can enhance brain circulation, prevent amyloid accumulation, and increase amyloid clearance	NILVAD (NCT02017340; phase 3)	500 people aged ≥ 50 years with mild-to-moderate AD dementia	18 months (completion in 2017)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can counteract amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)

(Table 13 continues on next page)

Mechanism		RCTs	Participants	Duration
(Continued from previous page)				
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
AZD0530 (saracatinib)	Fyn-kinase inhibitor: attenuates amyloid-mediated and tau-mediated neuronal damage	NCT02167256 (phase 2)	152 people aged 55–85 years with mild AD dementia	1 year (completion in 2016)
Masitinib (AB1010)	Selective tyrosine-kinase inhibitor: modulates neuroinflammation by regulating mast cell activity, and promotes neuroprotection by targeting Fyn kinase	NCT01872598 (phase 3)	396 people aged ≥50 years with mild-to-moderate AD dementia	6 months (completion in 2016)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. AMBAR=Alzheimer's Management by Albumin Replacement. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. ELAD=Evaluating Liraglutide in Alzheimer's Disease. MAOB=monoamine oxidase B. 5-HT=5-hydroxytryptamine. NMDA=N-methyl-D-aspartate. ADMET2=Apathy in Dementia Methylphenidate Trial 2. GM-CSF=granulocyte-macrophage colony-stimulating factor. ATP=adenosine triphosphate. RAGE=receptor for advanced glycation end-products. NILVAD=Nilvadipine in Mild to Moderate Alzheimer's Disease. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. * Age not provided. †A previous meta-analysis of six RCTs suggested beneficial symptomatic effects in people with mild-to-moderate dementia due to AD.³⁹⁰

Table 13: Drugs in late-stage clinical development for Alzheimer's disease in patients with dementia

work-ups will probably shift from mild AD and prodromal AD to preclinical AD (section 6). This shift is likely to have two implications, first for the validity of early-stage or preclinical diagnoses, and second for the long-term cost-effectiveness of treatment.

Biomarkers will be crucial for diagnosis, but have yet to be validated. Even if they were validated, available biomarkers would need to have high levels of sensitivity and specificity (eg, 95–99%) to be clinically useful. The risk of false-positive and false-negative cases needs to be considered carefully.⁴⁰⁰ Predictive biomarkers are needed to facilitate the diagnostic process. For example, no evidence exists to suggest that a patient with mild memory impairment will evolve differently from one with worse impairment, or that one with a small hippocampus or low CSF Aβ concentrations will respond to treatment better than a patient with a larger hippocampus or higher concentrations. Furthermore, the prognostic value of biomarkers such as Aβ and tau is unclear in very advanced age, and 70% of dementia cases in the general population are in people aged 75 years or older.

Estimating the long-term cost-effectiveness of available drugs is a challenge (section 1), and the duration for expected effects of treatment will be prolonged by many years with a shift to earlier-stage diagnoses, such as preclinical and prodromal AD. Furthermore, resource use and costs during the pre-dementia period are low, and conventional trials such as RCTs will not be useful for cost-effectiveness assessments. Other strategies, such as simulations or the use of registry data, will probably be better options for such assessments.

Population ageing is occurring worldwide, led by the demographic transition that has already happened in many European countries and in Japan. Ageing adds additional challenges in terms of early diagnosis, because of our unclear understanding of the threshold between age-related and disease-related cognitive decline. Another

problem in developing drugs for AD dementia is the multifactorial nature of dementia in old individuals, including concurrent vascular dementia and different types of neurodegenerative lesions. Physical comorbidity is also frequent in advanced age, generally accompanied by poly-pharmacotherapy, with non-optimum use of drugs for patients with AD (eg, anticholinergic and sedative effects are common and undesirable in geriatric patients with AD).^{401,402}

These challenges highlight the importance of offering a comprehensive geriatric assessment to every elderly patient—a multidisciplinary diagnostic and treatment process that could identify medical, psychosocial, and functional limitations of a frail elderly person, with the aim of developing a coordinated care plan to maximise overall health with ageing.^{403,404} Comprehensive geriatric assessment can support the assessment and management of people with dementia, improving pharmacological treatment decisions. Additionally, optimum management of multimorbidity can have benefits for cognition.

Existing and future regulatory processes

The unique challenges inherent in the development of drugs for AD and other dementias have driven regulatory policy. Guidance documents from the EMA^{405,406} and the FDA^{407–409} in the area of AD and other neurodegenerative diseases have considered a range of relevant issues: the potential effect of new diagnostic criteria for AD (the NIA-AA^{325–327} and IWG^{328–330} criteria) on trial design, and the development of drugs for treatment of early-stage disease; the choice of outcome parameters in clinical trials and the need for distinct assessment methods at different disease stages; the validation and potential use of biomarkers for different phases of AD in different stages of drug development; the design of long-term efficacy and safety studies; the design of studies of the usefulness of combination therapy; and the use of expedited

programmes for new treatments in drug development, such as fast-track designation or accelerated approval. Lessons learned from the challenges and successes of ongoing and future clinical trials in well-defined groups of participants at the preclinical, prodromal, or dementia stages of AD should lead swiftly to appropriate changes in regulatory policy. Moreover, harmonisation of the rules for drug approvals by the EMA and the FDA could help to accelerate the availability of promising new drugs.

Challenges in drug development

The evidence generated so far from clinical trials of drugs for AD is limited by the underlying assumptions and theories implicit in the generation of the data. The conceptual models for age-associated cognitive impairment, dementia syndrome, and AD need to be developed further, with a consideration of their effects on drug development. The causes of AD have yet to be elucidated: it is a complex disease, and formidable barriers to treatment research need to be overcome.

The several AD-related clinical diagnoses, including mild cognitive impairment due to AD, prodromal AD, and AD dementia, result in biologically and clinically heterogeneous groups of patients. In each group, patients vary in their cognitive profiles, severity of early memory impairments, genotypes, and expression of putative biomarkers. This heterogeneity makes drug discovery and development more complicated, and efforts are needed to subtype patients (eg, on the basis of biomarker profiles) such that groups with homogeneous aetiology and outlooks can be included in clinical trials. Similar efforts should be made for the range of age-associated conditions of cognitive impairment and other neurodegenerative disorders beyond AD.

Diagnostic criteria can have a substantial effect on the numbers of people recognised as having AD or other dementias, including those who are treated in clinical trials. The absence of validated drug targets and the large number of targets can lead to ethical challenges in clinical drug development. Many drug targets might be applicable to cognitive ageing or brain ageing, and to cognitive decline associated with AD. Moreover, substantial numbers of people in subgroups of the AD population probably won't be helped by any particular treatment. The identification of targets and development of safe therapeutics that can be used for very early intervention to prevent dementia in at-risk people is a priority.

So far, drugs in development for AD have each targeted and altered one aspect of the disease or one facet of brain function, but they have also adversely or unpredictably altered other aspects of brain function. Relating mechanisms of drug action to clinical outcomes is one challenge that needs to be addressed. The designs and outcomes of clinical trials have so far tended to be nearly identical from one programme to the next, and not necessarily relevant to the modelled action of the drug in question. Long clinical trials that use soft or

uncertain clinical and biological endpoints are obstacles to progress; targeted, efficient trial designs with optimum assessment of outcomes are needed to enable the individualisation of treatment. Decisions on the right drug for development, for the relevant groups in society, should be taken carefully, and not before the ultimate aims of treatment in the general population have been set.

A new clinical trials infrastructure is needed to avoid delays and barriers to recruitment, which are a major problem at present. Samples of convenience (eg, those that are not typical of everyday clinical practice) might not constitute valid trial samples for many purposes. For example, the median age at onset of dementias and AD is 80 years or older, in people who have substantial concomitant illnesses, and neuropathology is usually mixed.^{410,411} However, clinical trials are frequently done with much younger patients (eg, around 70 years) who have little concomitant illness and are taking few drugs, and attempts are made in recruitment to exclude other causes of cognitive impairment. The real benefit of anti-AD drugs for elderly patients needs to be established in clinical trials that take into account the mixed nature of the brain damage and neurodegeneration causing dementia, the impact of other illness, and the effects of poly-pharmacotherapy on cognition. The careful selection of participants would make trial results more generalisable to the general population.

Major barriers to progress include the limitations of current animal models of disease and translation of findings from preclinical studies to humans (section 5). New approaches to prevention trials, stratified medicine, and smaller phase 2a trials to gain early signals of potential efficacy might be helpful. In clinical research, the risks faced by participants are higher in the early phases of trials than in late phases, so a concentration of risk assessment and resources on early-phase research is essential. The substantial challenges involved in drug development for AD and other dementias demand a collaborative rather than a competitive effort, and all data from clinical trials should be made publicly available. Panel 5 provides a summary of steps that could be taken to improve the clinical-development enterprise.

Many reasons for the failures of clinical trials and drug-development programmes in AD have been advanced, but the most likely explanation for the absence of effective medications is that the drugs do not work. When truly effective drugs are tested, their effects will overcome the current inefficiencies in clinical development.

Prospects and goals for experimental treatments

Establishment of validated drug targets necessitates greater understanding of neurodegenerative diseases, other age-related syndromes of cognitive impairment, cognitive impairment associated with other disorders, and the numerous processes that lead to illness in these

conditions. Advances in basic and clinical science, including better knowledge and selection of drug targets, will drive future drug development. Although the amyloid cascade hypothesis of AD has dominated the specialty, basic and clinical research efforts need to assess the promise of other targets in different subgroups of patients at different disease stages. Advances in drug development and clinical trials will be incremental and iterative. Several failures in clinical development for AD have led to progress, with improved prospects for the identification of effective drugs. However, predictions of an effective treatment in the near future can be based only on the drugs in development at present, preclinical evidence, and the interest of experts and investors.

Summary and recommendations

An effective treatment for AD is perhaps the greatest unmet need facing modern medicine. An organised and concerted effort among governmental agencies, academic researchers, and industry will be needed to develop effective and affordable therapies. The overall success rate of drug development for AD has been poor. A few drugs are approved for the symptomatic treatment of dementia, and several drug candidates are in clinical trials, but novel paradigms are needed to incorporate advances in early diagnosis, genetic factors, and epidemiology into the design of clinical trials for new drug candidates. Major long-term financial commitment to clinical development will be essential.

(1) Improvements in the clinical-development infrastructure are needed, with increased collaboration between governments, public and private institutions, AD associations, and the pharmaceutical industry to facilitate clinical research. Substantial redundant research in AD drug development should be avoided.

(2) Increased research budgets are needed for drug discovery, drug development, and clinical trials. International cohorts, standardised methods, and ethical and regulatory frameworks should be established to facilitate clinical studies. Clinical drug development and clinical trials should be coordinated internationally. New approaches to drug development (eg, for different treatment aims) should be recognised and supported.

(3) Public, private, and corporate funding decisions should be based on evidence and scientific merit, rather than being driven by advocacy, opinion, persuasion, or corporate considerations.

(4) The voice of patients should be strengthened in risk-based approaches to the conduct of early first-in-human clinical trials in which the preclinical evidence base is weak. Options should be discussed for earlier entry of patients into clinical-development programmes, enabling the collection of valuable pharmacokinetic and pharmacodynamic information from participants. This approach would help to refine adaptive clinical trials and enable early failure.

Panel 5: Clinical-development enterprise for Alzheimer's disease

- Drugs are needed to both prevent and treat the cognitive and functional symptoms of preclinical Alzheimer's disease (AD), prodromal AD, and AD dementia.
- Plans are needed to decide which drugs to support in clinical development and to identify the determinants of successful translation of experimental drugs to AD treatment.
- More resources are needed for early clinical development so that more potential treatments can be assessed. Resources should be directed to areas where there is evidence of efficacy. Clinical development should be justified by previous knowledge that indicates the likelihood of success.
- Detailed results and outcomes of clinical trials should be made broadly available immediately after studies have been completed in a manner that is accessible to the general public. Protocols for clinical trials should be published.
- Preclinical research and early-phase clinical trials need to be replicated before drug development moves to later phases. People at risk of AD and patients with the disease should not be enrolled in trials that have a high risk of failure. The emphasis on phase 3 without fulfilling the objectives of phase 2 is wasteful and not justifiable from a societal perspective (although high-risk, high-rewards business arguments have been made for these wagers).
- Careful assessments are needed to decide whether or not clinical research is worth pursuing. For example, is an expected 1.5 point change on the Alzheimer's Disease Assessment Scale–cognitive subscale after 2 years of treatment worthwhile, or might efforts be better spent elsewhere? The capital put into the unsuccessful bapineuzumab and solanezumab phase 3 programmes could have funded perhaps 20 focused phase 2 development programmes for a range of compounds with different mechanisms, the outcomes of which would have provided more information than those for just two drugs.
- Collaborative risk-sharing among governments and industry should be considered. Failures of very large programmes can have devastating effects. Treatment approaches with common mechanisms could be developed collaboratively rather than competitively. There is a societal need to reduce redundant approaches and competition between similar approaches.

(5) More patients should be invited to participate in research. Registries of elderly patients with and without cognitive impairment are needed to facilitate recruitment into trials.

(6) A more synchronised approach is needed for the implementation of regulatory processes for the conduct of clinical trials in national laws.^{412,413}

Section 8. Non-pharmacological interventions for dementia and mild cognitive impairment

Although considerable efforts have been made to improve understanding of the neurobiology of AD (section 5) and to identify and evaluate candidate disease-modifying therapies (section 7), far less effort has been focused on the development and implementation of non-pharmacological interventions. Insufficient focus on these approaches represents a missed opportunity, because the identification of effective non-pharmacological interventions for key indications is a much more tractable short-term target than is the development of effective drugs, and efforts in this area are likely to lead to tangible benefits that will help people

to live better with dementia. Specialist terms used in this section are defined in panel 3.

Non-pharmacological interventions for dementia

Cognitive training and brain-training games

The aim of cognitive training and brain-training games is to provide individuals with strategies to improve cognition. Generally, such interventions follow one of two approaches: strategies based on theoretical neuropsychological models of cognition or learning (eg, errorless learning), or the teaching of skills to improve specific aspects of cognition (eg, mnemonic strategies to improve new learning). These interventions, which include computer-based approaches, can be delivered to individuals or to groups. A meta-analysis of ten (mainly small) RCTs that focused on healthy older individuals (age 60–76 years across the studies) indicated a small but significant benefit (effect size 0.15, 95% CI 0.103–0.194), which was generally limited to the specific cognitive domain targeted by the training.⁴¹⁴ A common weakness of many such studies is that the comparison has been no treatment—ie, no active control. In such circumstances, the comparison group will not benefit from the non-specific advantages associated with any intervention due to placebo and Hawthorne effects. The consequence is that the comparative benefits of the intervention under investigation can be exaggerated.

The largest and most extensive study, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial,⁴¹⁵ followed up more than 2500 cognitively healthy older adults aged 65 years or older (mean age 74 years) during 5 years at six US sites. Participants received training focused on attention, memory, or reasoning in ten group sessions, with follow-up booster training over the course of the study. Participants learned specific mnemonic (organisation, visualisation, and association) strategies and reasoning strategies (eg, teaching strategies to find a pattern in a letter or word series) to improve cognitive performance in the respective intervention groups. Benefits were reported in the cognitive domain that was the focus of the specific training package, with improvements in memory after memory training, and improvements in attention after attention training. Only reasoning training had the added benefit of more general improvements in memory and attention as well as reasoning, and conferred additional benefits on IADL.⁴¹⁵ Further work is needed to examine the cost-effectiveness of cognitive training in healthy older people.

Findings from studies of the benefits of cognitive training in people with memory impairment or dementia are more conflicting. In the ACTIVE study, memory training conferred no benefit in the subgroup of individuals with memory impairment (based on a threshold of 1.5 SD below normative values on the Rey Auditory Verbal Learning Test). Cognitive training in people with AD has been assessed in 11 RCTs, which mainly had fewer than 50 participants. Out of eight studies reviewed for general cognitive outcomes (MMSE or ADAS-Cog) in a systematic

review, three showed significant benefits.⁴¹⁶ However, neither of the trials that were judged to be high quality by the reviewers reported a significant advantage of cognitive training. Several studies reported benefits in at least one specific aspect of cognition, but without any consistency in cognitive domains across studies. The authors of the systematic review did not do a meta-analysis because of the huge variability in the cognitive outcomes measured across the studies, so the effect size and overall significance of reported cognitive benefits have not been elucidated. They concluded that there was sufficient evidence of benefit provided by cognitive training to merit further, larger intervention studies.⁴¹⁶

Many commercial companies have developed and marketed brain-training games. Despite the publicity surrounding the benefits of such games, little evidence exists to support the value of any of the commercially available products. By far the largest intervention study of brain training is Brain Test Britain,⁴¹⁷ a 6 week online study with 11430 participants aged 18–60 years who were randomly assigned to receive brain training in reasoning (with an emphasis on training games involving executive function), general brain training (similar to commercially available brain-training games), or control (internet search tasks). On average, participants completed 24 training sessions during the 6 weeks of the intervention. Participants showed a large and significant improvement in performance in the actual brain-training games (Cohen's *d* standardised effect size 0.73, 99% CI 0.68–0.79, and 0.72, 0.67–0.78, respectively, for the two active interventions), but these improvements were not translated to significant benefit in standardised cognitive assessments of executive function, attention, or working memory.⁴¹⁷ Longer-term outcomes have been reported for the older participants in the study (6742 adults older than 50 years), including significant benefits in reasoning, verbal learning, and IADL over 6 months with reasoning training and general brain training compared with the control treatment, but with substantial numbers of dropouts after 12 weeks.⁴¹⁸

The largest RCT of cognitive rehabilitation assessed 69 people with AD or mixed AD and vascular dementia who had MMSE scores of more than 18.⁴¹⁹ Participants were randomly assigned to three arms for 8 weeks: the first group (n=23) received a cognitive-rehabilitation intervention to improve individualised outcomes, an active control group (n=24) received relaxation and stress management, and the third group (n=22) received no treatment. The multifaceted cognitive-rehabilitation approach consisted of weekly individual sessions with use of teaching strategies and techniques for learning new information, maintaining attention and concentration, managing stress, and using appropriate aids. The cognitive-rehabilitation intervention was associated with significant improvement in ratings of goal performance and satisfaction, whereas scores were unchanged in the control groups. Smaller case series

have also shown improvements in global ADL measures with the use of interventions based on implicit memory.⁴¹⁹

Although the idea of cognitive stimulation for people with dementia is not new, Spector and colleagues were the first to develop this approach into a standardised treatment.⁴²⁰ Their intervention, cognitive stimulation therapy (CST), is a group-based approach for people with mild-to-moderate dementia that is based on the theoretical notions of reality orientation and cognitive stimulation. The therapy takes a very specific, operationalised approach, with 14 sessions of themed activities that typically run twice a week during a 7 week period.⁴²⁰ In a single-blind RCT of CST in 201 people with dementia (115 receiving CST and 86 controls),⁴²¹ significant improvements in MMSE ($p=0.04$) and ADAS-Cog ($p=0.01$) scores were reported in the treatment group compared with the control group, with additional benefits in quality of life. These initial cognitive improvements after CST were sustained with maintenance CST.⁴²²

The cost-effectiveness of CST was examined in an RCT in people with mild-to-moderate dementia, in which 91 people received CST and 70 were given care as usual. Costs were calculated for the 8 weeks before and the 8 weeks after treatment. Cost-effectiveness analyses usually calculate the cost of improving quality of life, with outcomes such as QALYs (section 1). A health-economic analysis⁴²³ indicated that CST has quality-of-life advantages without incurring additional cost, suggesting that CST is a cost-effective intervention. The positive effect of CST on quality of life has been further supported by qualitative studies.⁴²⁴ Other research groups have adopted a broader definition of cognitive stimulation, and developed other interventions that are less operationalised than the package of CST developed by Spector and colleagues. However, the overall evidence base for these alternative approaches is less clearcut than that for the original package of CST.^{425,426}

The important role of caregivers

Caregivers have a crucial part to play in the treatment of patients with AD. Caregivers' reports about patients' cognitive impairment correlate better with objective neuropsychological assessments than do patients' own complaints.⁴²⁷ Furthermore, people with pre-symptomatic or preclinical AD whose caregivers identify that they have cognitive complaints are more than twice as likely to progress to dementia than are people with caregivers who do not report such complaints (OR 2.2, 99% CI 1.2–3.9; $p<0.001$), suggesting that carers can accurately identify significant levels of cognitive dysfunction.⁴²⁸ Caregivers generally provide a more accurate longitudinal history and more precise information about daily function than can be gleaned from an office consultation with the patient. Importantly, they can often provide proxy consent for treatment and for trials when patients are insufficiently competent to give consent themselves. All drug trials for AD require an informant with a specified minimum

amount of weekly contact. Caregivers can help to ensure compliance, monitor outcomes, and report adverse effects.

In addition to being part of the therapeutic team, caregivers can become therapists themselves through the use of cognitive stimulation techniques,⁴²⁹ and by managing behavioural and psychological symptoms of dementia.⁴³⁰ Drug treatment for patients with AD can secondarily benefit carers in reducing their time commitment for supervision and assistance with daily care.^{431–433} Nevertheless, caregivers often experience substantial subjective and objective burden, with high levels of stress and mood disorder, and they are at increased risk of alcohol-related problems and medical comorbidity. Provision of support for caregivers is therefore essential for their wellbeing and to enable the best care for people with dementia. Non-pharmacological interventions play a key part in reducing stress and improving wellbeing in caregivers themselves. Several small RCTs of group cognitive behavioural therapy for caregivers and educational programmes that include skill training have shown significant improvements in the mental health and coping skills of caregivers.^{434,435} Educational interventions without these components, carer support groups that do not use cognitive behavioural therapy, and information provision without other key elements are associated with less convincing evidence of benefit.⁴³⁶

Information provision

Information is a key aspect of service provision to people with dementia and those caring for them, and the importance of information and signposting is often presented as a benefit of early diagnosis. Information can cover a broad range of topics, including the symptoms and causes of dementia, drug therapies and other treatment approaches, and more detailed information about specific symptoms and their treatment and management. Other topics include the effects of dementia on caregivers, financial information (eg, available financial support), key legal issues, and guidance about advance directives. Some sources also address local service provision, providing information about charities and local groups that can signpost caregivers and people with dementia to the support that they need.

In a systematic review,⁴³⁶ 13 RCTs were identified that focused predominantly on the provision of information, although many included additional elements such as skills training, telephone support, and direct help to navigate the medical and care system. Two of the three studies in which quality of life was measured indicated modest but significant benefits of information provision in people with dementia, and significant benefits were also evident for neuropsychiatric symptoms. However, a meta-analysis of the same 13 studies did not show any significant benefit for caregivers with respect to caregiver burden. Although this evidence provides some support for the value of information services, further studies are

For more on **cognitive stimulation therapy** see <http://www.cstdementia.com/>

needed to determine the specific elements that are effective and to optimise interventions. The design of such studies will be challenging, because it would not be ethical to deprive individuals of the usual sources of information. However, these studies, including a health-economic component, will be essential to enable international standards to be set for the development and implementation of optimum and cost-effective information-provision services.

Treatment of neuropsychiatric symptoms

The three main types of difficult-to-manage neuropsychiatric symptoms in patients with dementia are agitation, psychosis, and mood disorder. Agitation includes symptoms of aggression, irritability, restlessness, shouting, and pacing, usually in the context of distress or anxiety. The most frequent psychotic symptoms are visual hallucinations, auditory hallucinations, and persecutory delusions. First-rank symptoms of schizophrenia almost never occur in individuals with dementia, and the psychotic symptoms seen in dementia are much less complex than those associated with functional psychoses—usually visual or second-person auditory hallucinations of people or animals, and simple persecutory delusions such as believing that possessions have been stolen. Mood disorders include depression, anxiety, and apathy.⁴³⁷

A review of neuropsychiatric symptoms in AD was done in 2010 under the auspices of the Neuropsychiatric Syndromes (NPS) Professional Interest Area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART).⁴³⁷ The review stated that "treatment development should not be limited to pharmacological interventions... Treatment developments must take into consideration neurobiological and psychological contexts of the development and manifestations of NPS in AD."^{438–441}

In a systematic review⁴⁴² of the value of personalised psychosocial interventions to address behavioural and psychological symptoms in people with dementia living in care-home settings, the substantial evidence in favour of pleasant activities with or without social interaction for the treatment of agitation was highlighted. Well established interventions include the Seattle protocols, which focus on the assessment of person-centred activities and the introduction of a care plan to ensure that individuals receive at least 60 min a week of enjoyable activities, with an additional focus on problem solving to maximise implementation;⁴⁴³ and the approach for person-centred social interaction developed by Cohen-Mansfield and colleagues.⁴⁴⁴ The review also showed the value of reminiscence therapy to improve mood.⁴⁴²

A meta-analysis of RCTs of person-centred care training also showed the value of specific training approaches to improve agitation and reduce antipsychotic medication use in people with dementia living in care homes.⁴⁴⁵ The Improving Well-being and Health for People with Dementia (WHELD) trial,⁴⁴⁶ which combined

person-centred care with person-centred activities and exercise, also showed the potential for this intervention to reduce mortality and antipsychotic use and improve neuropsychiatric outcomes. However, in the studies published so far, such training interventions did not improve measures of wellbeing and quality of life for people with dementia.⁴⁴⁵ Further work is therefore needed to optimise training interventions to deliver significant quality-of-life improvements, perhaps by using specific elements for the implementation of evidence-based non-pharmacological interventions, in addition to more generic training to promote person-centred care.

Wellbeing and quality of life in nursing-home care

The numbers of people with dementia living in care homes have not been calculated on a Europe-wide basis. In the UK, about 250 000 of the 750 000 people with dementia reside in care homes.⁴⁴⁷ As the age and dependency characteristics of people with dementia are similar across Europe,⁴⁴⁷ it seems likely that roughly 1·6 million European citizens are living with dementia in care homes, with a median spend of 1% of GDP on long-term care across Europe.⁴⁴⁸ Admission to a nursing home for old people with AD is associated with a reduction in the range of life roles. For example, people are usually less involved in the management of their financial affairs and might be less engaged with family, friends, and hobbies outside the care-home environment. Individuals might also find that engagement in meaningful activities within the care home is diminished. Life in nursing homes is often depicted in terms of boredom, loneliness, and a disconnect between previous roles and interests and ongoing engagement in meaningful activities.

In a large observational study⁴⁴⁹ that used dementia care mapping to assess the quality of care in private-sector and UK National Health Service facilities, participants spent less than 2 min of a 6 h daytime observation period engaged in direct social interaction, and spent much of the time withdrawn. Contemporary nursing-home care in Europe and North America is often criticised for being task oriented and strongly focused on functional and biomedical needs, despite research suggesting that best-practice nursing-home care involves a health-promoting approach that addresses psychosocial and existential needs through resident engagement in individualised, meaningful activities.^{450–453} Research shows that people with AD and other dementias in nursing homes generally have little opportunity to participate in such activities.⁴⁴⁹

In the previous subsection, we briefly described the potential benefits of personalised activities as a treatment approach for neuropsychiatric symptoms. A strong body of evidence also points to beneficial outcomes from interventions that promote engagement in activities adapted to the patient's cognitive and functional abilities, including improved quality of life and wellbeing, reduced anxiety, better attention, and increased alertness.^{451,454–460} The essence of nursing-home care is to compensate for

For more on ISTAART see

<https://act.alz.org/site/>

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cognitive and functional losses by assisting patients in meeting basic human needs, including active or passive social engagement and participation. From an existential perspective, engaging in meaningful activities also helps to represent and define individuality, and to support a sense of self. Such engagement might simply mean passive participation in, or observation of, familiar and everyday activities, rather than the use of wide-ranging activity programmes. Interventions that promote activities and an increase in vocational tasks improve wellbeing and quality of life, in addition to neuropsychiatric symptoms.^{450,461–464}

Natural products and medical foods

Studies of the potential benefits of natural products and medical foods in AD have not yielded positive results. Initial studies of ginkgo biloba, the most extensively studied product, suggested modest but significant improvements in cognition, but the results were not replicated in larger and more robust studies, and the overall evidence does not suggest that the product offers any significant benefit.⁴⁶⁵

Intervention studies of vitamin supplements or medical foods containing vitamins have generally been disappointing. In a study of Souvenaid (Nutricia, Zoetermeer, Netherlands),⁴⁶⁶ a nutritional drink that contains vitamins and other components with the aim of neuroprotection, 225 patients with mild AD were randomised to Souvenaid or a control drink, taken once daily for 12 weeks; the primary outcome measure was a composite neuropsychological assessment battery. Souvenaid did not confer significant benefit on overall cognitive performance, and was associated with only very slight benefits on select areas of cognition, mainly memory. Additionally, Souvenaid did not offer any improvements in everyday functioning compared with placebo.⁴⁶⁶ Thus, the evidence of benefit for Souvenaid did not meet the usual standards for a recommended therapy.

The Homocysteine and B Vitamins in Cognitive Impairment (VITACOG) study⁴⁶⁷ examined vitamin B12, vitamin B6, and folic acid supplementation in 271 people with mild cognitive impairment. No significant benefit with respect to neuropsychological performance or the rate of brain atrophy was found for the whole group. However, some evidence of benefit was noted in a post-hoc analysis that focused on the subgroup of people with high plasma concentrations of homocysteine (a homologue of the amino acid cysteine) at baseline. Benefits in this subgroup seem biologically plausible, because raised homocysteine is associated with low concentrations of vitamin B12 and folic acid, and has been linked to increased risk of vascular damage and dementia.⁴⁶⁷ Further studies are needed to confirm whether or not B vitamins and folic acid are beneficial in people with pre-symptomatic or preclinical AD and raised homocysteine concentrations.

Vitamin E is the only other vitamin-based treatment with some clinical trial evidence of potential benefit. The

Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)⁴⁶⁸ examined the efficacy of memantine and vitamin E (α -tocopherol; 2000 IU per day), alone or in combination, in people with mild-to-moderate AD who were already taking acetylcholinesterase inhibitors. A significant and potentially important overall clinical benefit, equivalent to 6 months of natural decline, was shown for vitamin E compared with placebo for the primary outcome, ADL. However, no benefit was reported for the group receiving both vitamin E and memantine, or for any of the secondary measures, including cognition.

Previous RCTs of vitamin E have also produced mixed results. A large RCT in people with preclinical or prodromal AD (diagnosed on the basis of criteria for mild cognitive impairment without biomarkers) suggested no benefit.⁴⁶⁹ However, the Alzheimer's Disease Cooperative Study (ADCS)⁴⁷⁰ of 341 patients with moderate-to-severe disease did show significant benefits for vitamin E on the primary outcome, a composite measure of poor outcome. However, although two well done RCTs (ADCS and TEAM-AD) have shown benefits of vitamin E on the primary outcome measure, the interpretation or understanding of global benefit is difficult in the absence of evidence for specific benefits on cognition or function. Additionally, because the dose of vitamin E used in these studies is ten times higher than that usually sold as a food additive, potential safety issues need to be considered. For these reasons, the use of vitamin E as a clinical treatment for AD is not recommended at present.

Fatty acids have also been a focus of interest in AD. Two large multicentre RCTs, each with more than 150 participants, showed no significant benefits of omega-3 fatty acid treatment, including docosahexaenoic acid supplementation, on cognition, everyday activities, or global outcomes.^{471,472} Although there has been media interest in ketogenic treatments such as Axona (Accera, Broomfield, CO, USA), the only published clinical trial—a multicentre phase 2 RCT in 152 people with mild-to-moderate AD—did not show any significant benefits on cognition or other outcomes after 90 days.⁴⁷³ The theory that ketones could provide an alternative energy source for the brain is predicated on the unproven assumption that the brain's ability to use glucose is impaired in AD.

Generally, very little efficacy or safety evidence is required for the marketing of food additives, which can have an unfortunate role in creating false expectations among consumers, and could potentially lead to unforeseen safety issues. For example, a meta-analysis showed that antioxidant supplements might be associated with increased mortality risk,⁴⁷⁴ and another meta-analysis of RCTs provided evidence that vitamin E supplementation is associated with increased mortality and an increased risk of haemorrhagic stroke.⁴⁷⁵

Although promising results have been reported in cohort studies of the potential benefits of the Mediterranean diet,⁴⁷⁶ these results might be confounded

For more on the ADCS initiative
see <http://adcs.org/>

by other elements of healthy living, and a randomised intervention study is needed in people with mild cognitive impairment and mild dementia.

Non-pharmacological interventions for people at risk of dementia

Many studies of lifestyle and other non-pharmacological interventions to prevent or delay the onset of dementia in people with preclinical AD have been done (section 3), mostly in people with amnesic impairments in whom AD biomarkers have not been assessed. Evidence for any benefit of social activity, weight maintenance, or diet is inconsistent or very preliminary.⁴⁷⁷ The pivotal FINGER study of people aged 60–77 years¹⁸⁹ showed significant benefits of a multidomain intervention (diet, exercise, cognitive training, and management of vascular risk factors) on overall cognitive function, compared with a control treatment (general health advice), with the largest benefits seen for attention and executive functions. This 2 year RCT provides key proof of concept that multidomain trials are feasible and that such approaches can confer cognitive benefit. However, further studies are needed to ascertain which elements contributed to the reported benefits, and to understand and improve the cost-effectiveness of the intervention, which was originally delivered as three separate interventions with a total of more than 30 therapy sessions, in addition to self-directed interventions.

Strong evidence exists to support smoking cessation in people at risk of AD,⁴⁷⁷ which is already widely implemented, and the benefits of cognitive reserve,⁴⁷⁸ although this would need to be implemented as part of educational policy across the life course because the development of cognitive reserve is based largely on childhood cognition and educational attainment, together with occupation in adult life.

Several small and medium-sized trials have investigated the effects of exercise specifically in people with subjective memory problems, mild cognitive impairment, or preclinical or prodromal AD. The main studies have identified participants on the basis of amnesic deficits or subjective reports of memory difficulties in the absence of AD, and alterations in AD biomarkers were not required. The largest trial,⁴⁷⁹ which was undertaken in Australia and included 170 adults with subjective memory complaints, 92 of whom had mild cognitive impairment, showed a significant advantage of a 6 month programme of physical activity on cognitive function (the primary outcome was change in ADAS-Cog score at 6 months' follow-up). Benefits were maintained for 18 months and were more pronounced in people with mild cognitive impairment. Additional benefits were noted in global outcome.⁴⁷⁹ Several exploratory trials of aerobic exercise in people with mild cognitive impairment, most of which assessed a range of measures without stipulating a primary outcome, have also reported significant improvements in cognition, function, cardiovascular

fitness, motor performance, brain plasticity, and AD biomarker concentrations,^{480–483} and a systematic review has concurred that aerobic exercise provides cognitive benefits in people with preclinical or prodromal AD.⁴⁸⁴

The evidence is already strong, but larger and better-powered RCTs are now needed in people with preclinical or prodromal AD to determine whether exercise can delay conversion to symptomatic AD, provide evidence about cost-effectiveness, and inform practice. Several studies are examining the potential of multicomponent interventions, including exercise, to prevent dementia in people with cognitive impairment and vascular disease or vascular risk factors—eg, Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN; NCT01573546), Aerobic Exercise Training in Mild Cognitive Impairment Study (AETMCI; NCT01146717), Pioglitazone Or Exercise to Treat Mild Cognitive Impairment (POEM; NCT00736996), and Community-Based, Buddy-Supported Exercise in Patients with Mild Cognitive Impairment (My Buddy Study; NCT01561820). These trials will improve understanding of the cost-effectiveness of interventions, the potential additive benefits of multicomponent interventions, and the specific groups of individuals who might derive optimum benefits. However, exercise already has a better evidence base than any other pharmacological or non-pharmacological intervention for people with preclinical AD, and a strong case can be made that we should be offering exercise interventions routinely as a core part of the clinical management of individuals at risk of dementia. The public health impact could be substantial: a review¹¹ of the relative risk of incident dementia in 16 longitudinal cohort studies calculated that a 25% reduction in inactivity could prevent up to 1 million people from developing AD worldwide.

Implementation of non-pharmacological interventions

One of the most disappointing aspects of non-pharmacological interventions to treat or prevent dementia is that they are rarely systematically implemented in clinical and care practice, even when there is clear evidence of benefit from RCTs. For example, although opportunities exist to further optimise the benefits of person-centred care training in nursing homes, clear evidence already shows that several specific interventions to improve person-centred care (eg, focused intervention training and support [FITS] and dementia care mapping) can help with neuropsychiatric symptoms and enable a reduction in antipsychotic use. However, a 2014 survey of available person-centred care interventions in the English language showed that only three of 170 interventions (1.8%) were supported by clinical-trial evidence of benefit.⁴⁴⁵ Many training programmes have been developed by private companies and have not been assessed to establish whether or not they benefit people with dementia. Interventions that are known to be

For more on the **ENLIGHTEN trial** see <http://sites.duke.edu/enlighten/>

For more on the **AETMCI study** see <https://www.nia.nih.gov/alzheimers/clinical-trials/aerobic-exercise-training-mild-cognitive-impairment>

For more on the **POEM study** see <https://www.nia.nih.gov/alzheimers/clinical-trials/pioglitazone-or-exercise-treat-mild-cognitive-impairment>

For more on the **My Buddy Study** see <http://www.wakehealth.edu/Research/Gerontology-and-Geriatrics/Kulynych-Center/Buddy.htm>

effective all involve a therapist working with care-home staff for a period of at least 4 months to reinforce the training, and although some of the unevaluated training programmes follow good educational principles, they do not generally have this additional component. Tighter criteria are needed that demand evidence of benefit for approved training programmes.

Further examples of failure to implement a non-pharmacological intervention with good clinical-trial evidence of benefit relate to the promotion of person-centred activities for people with dementia in nursing homes, and interventions to promote aerobic exercise in people at preclinical stages of disease, with general recommendations often being made without attention to detail or structure for implementation. A programme to train and support CST therapists has been developed by University College London, UK, and has enabled some use of CST in routine clinical practice within the UK, but further development of the training and support is needed to enable full international implementation of this intervention.

Challenges and opportunities

The 2013 G8 dementia summit emphasised the need for non-pharmacological interventions that are effective and safe and can be used worldwide.¹⁷³ Accordingly, our future vision is the routine implementation of evidence-based effective and cost-effective non-pharmacological therapies for the treatment of cognition, function, and neuropsychiatric symptoms, and caregiver support, coupled with a better understanding of the optimum combination of non-pharmacological and pharmacological interventions as a routine part of clinical care. Related to these aims is the need to fully harness the potential of caregivers as cotherapists to improve outcomes for people with dementia (section 9).

Further systematic review and international consensus are required to enable a blueprint for best practice and to identify the non-pharmacological interventions that should be routinely available as part of clinical care and key research gaps. The absence of a strong commercial interest in the development of non-pharmacological interventions has meant that funding for RCTs is difficult to obtain. Moreover, studies to examine the additive benefits of non-pharmacological and pharmacological interventions are time consuming, expensive, and difficult to undertake, as are large, adequately powered RCTs of personalised non-pharmacological interventions. There might be opportunities to streamline other non-pharmacological interventions, such as cognitive training and exercise, by using self-directed online interventions.

In the treatment of neuropsychiatric symptoms, the absence of clear research definitions for key symptoms, such as agitation, is an additional challenge, with different definitions used in different studies and with different assessment methods. A working group of the

International Psychogeriatric Association has been convened to develop an improved international consensus. High placebo response rates in clinical trials of neuropsychiatric symptoms—often higher than 40% and reflecting non-specific benefits, increased social and clinical interaction as part of study protocols, and spontaneous resolution of symptoms—are an additional challenge that needs to be addressed. Proposed solutions include the introduction of a less intense non-pharmacological intervention lead-in period for all participants, an increased symptom threshold for entry into trials, and the use of novel approaches (eg, central rating through video links) to reduce the number of raters and increase the inter-rater reliability for primary outcome measures.

Personalised activities for people with dementia living in nursing homes require a shift in culture, from doing for to doing with. The overall philosophy of care, organisational demands, and priorities can enable or obstruct resident engagement in activities and health promotion. Good-quality information must be widely available in Europe, and understanding of the added components of information and educational interventions that are necessary to confer benefit to people with dementia and those caring for them is essential.

Summary and recommendations

Non-pharmacological interventions and the active, early involvement of caregivers should be an integral part of AD treatment strategies. The diagnosis and treatment of associated conditions, neuropsychiatric symptoms, and psychosocial deterioration are key elements in improving the quality of life of patients with AD and their families. Lifestyle changes, exercise, and nutritional support might have a role at all phases of the disease, but more research is needed to guide the implementation of intervention programmes.

(1) Systematic reviews are needed and must be supported by an international Delphi consensus to establish which evidence-based non-pharmacological interventions should be available for patients in Europe and for what indications.

(2) European recommendations and an infrastructure to enable the use of non-pharmacological interventions for which clear evidence of benefit already exists should be put into practice with appropriate training, support, and maintenance of fidelity. Examples of such interventions include exercise, CST, personalised activities, person-centred care training in care homes, and activities (with or without social interaction) for the treatment of agitation.

(3) A European consensus on the highest-priority non-pharmacological interventions would be helpful in guiding reimbursement decisions in individual countries.

(4) Additional RCTs are needed to address key gaps in understanding and unmet needs of patients (eg, non-pharmacological management of sleep disturbance, pain, psychosis, and apathy in people with dementia).

For more on the **International Psychogeriatric Association** see <http://www.ipa-online.org/>

(5) Partnerships are needed between public funders and commercial organisations to address the funding challenge in studies of non-pharmacological interventions, to enable studies of the combination of key non-pharmacological and pharmacological interventions, and to facilitate academic–commercial collaborations.

(6) Open access to data from RCTs of non-pharmacological treatments is needed to support systematic reviews and meta-analyses based on individual patient data.

(7) Treatment manuals and caregiver training programmes for effective non-pharmacological interventions should be made generally available—eg, as part of dissemination by research groups involved in the development and assessment of such programmes.

(8) Non-pharmacological interventions and activities can have an inherent ethical value in high-quality care, even if the detection of measurable group-level outcomes is sometimes difficult. Ethical evidence, such as observed signs of wellbeing while a personally meaningful activity is ongoing, needs to be systematically collected, discussed, and used in clinical care.

Section 9. Formal and informal care for people with dementia

People with dementia need care and support in many areas of their lives. This support might be provided by health-care, social-care, housing, transport, leisure, or other sectors. Irrespective of the provider, support can be grouped into three main domains: support in basic ADL, support in IADL, and supervision to safeguard individuals from harm.⁴⁸⁵ In addition to these forms of care and support, individuals with dementia might receive care from specific medical services, such as injections, infusions, and medications to alleviate dementia symptoms. ADL are basic personal activities that include dressing, eating, toilet visits, personal-care activities, and moving around the home or a care facility. IADL relate to more complex activities with a social component, such as preparing food, shopping, managing money, laundry, cleaning the house, managing public transportation, and communication (eg, using the telephone). One challenge with IADL is that they are affected by context and more closely linked to technical abilities, such as use of mobile phones, the internet,⁴⁸⁶ or technical equipment in care.

The care and support provided for people with dementia often spans several sectors and does not fit easily into typical health-care delivery structures. The optimum approach for patients is not always in harmony with traditional ways of organising and financing formal care into distinct health-care and social-care categories. Traditional health care takes place in hospitals, specialist-care settings, and primary-care settings, and is provided by doctors, nurses, physiotherapists, occupational therapists, psychologists, and health-care assistants. Long-term care in nursing homes (or similar) or in the patient's home can be delivered by health-care or social-care

providers, or both. Similarly, day care can focus on social activities (social care) or physical rehabilitation (health care). Care at home is conventionally classified as formal (delivered by paid staff) or informal (delivered by unpaid family members or other carers), although the meaning and separation of these concepts is changing.

Most people with dementia will receive both formal and informal care during the course of their illness. Indeed, no health-care or social-care system in the world could meet the needs of people with dementia without these informal-care inputs. Consequently, the substantial contributions made by family members and other unpaid carers should be fully recognised in strategic policy discussions and in case-level planning and assessments, with a consideration of the opportunity costs for carers and the consequences for their health and quality of life.⁴⁸⁷

The distinction between paid staff and unpaid carers has been blurred as informal caregivers have become increasingly active in many parts of the care system, not only as providers of personal care but also as advocates, participants in care planning, and holders of devolved (personal) budgets (section 8).⁴⁸⁸ The growth of different forms of self-directed support has been a notable feature of many social-care and health-care systems; personal budgets pass responsibility for the management of care resources to the patient or carer, often with both effectiveness and cost-effectiveness advantages.⁴⁸⁹ However, by contrast with other chronic disorders, care planning and self-directed support are complicated in the case of dementia by the effects of cognitive decline (eg, loss of mental capacity, lack of insight, legal issues of impaired autonomy, and risks of financial abuse). Thus, strategies to close the gaps between all involved factors and participants—including clear political strategies (eg, national dementia care plans), case-management plans, counselling, and education—are crucial for quality of care.

The needs and demands of patients and their families cannot all be met by public-sector health-care and social-care agencies alone, even though the public sector tends to dominate in most European countries. Organisations in the voluntary sector (often called the charitable, non-profit, or third sector) and in the private (for-profit) sector have an important part to play. The voluntary and private sectors deliver mainstream services and engage in other activities, such as information provision, lobbying for better care or more research, and case-level brokerage. Some of these activities might be funded by government under contract or via (general) grant aid, but many will be funded through charitable donations or private-market transactions, in which care services are sold directly to people with dementia or their families. Whether such services can serve as complements to, or substitutes for, available public-sector resources will depend on national structures and local conditions. Moreover, how the quality and cost-effectiveness of such services compare with those of the public sector is unclear.^{490–492}

Formal (paid) care

Panel 6 provides a list of formal-care resources and activities, including support provided by staff in various settings, aids and adaptations, and newer technical support (eg, alarms and other forms of telecare). For the purposes of policy development, local planning and commissioning, and the regulation and monitoring of care, each activity should be measurable and quantifiable in some way (eg, hours, days, or number of visits). The definition of institution (as an alternative to home) varies widely. It could be a small, specialised group home for six to eight people with dementia, with staff trained in dementia care to provide round-the-clock support, a supervised facility with low staff-to-patient ratios, or a large nursing home with several hundred people with dementia and an emphasis on medical care. The wider concept of long-term care also includes comprehensive care at home.

The ultimate aim of high-quality formal care for people with dementia is the creation of an environment in which the individual's needs are met—where they are respected and have a sense of dignity, meaningfulness, and wellbeing, despite the various limitations imposed by the disease. Care needs to go beyond the provision of basic physical tasks and procedures (eg, eating, dressing, and hygiene) to include the creation and maintenance of a positive, person-centred environment and the support of patients' relationships. However, there is a risk that, of these two important dimensions of formal care, basic care tasks are given almost exclusive priority in financially constrained contexts, and that organisational decisions are so heavily influenced by financial considerations that only the minimum resources are made available to guarantee the most basic physical care. Ethical dimensions also need to be considered, even if outcomes such as dignity, meaningfulness, and wellbeing are difficult to assess. The processes of planning, organising, funding, delivering, and assessing formal dementia care need to support the completion of basic care tasks and enable high-quality care to meet the psychosocial and existential health needs of patients with dementia.

Informal (unpaid) care

Analysis of the circumstances of informal carers is complex (eg, including assessments of the needs and preferences of carers), and economic analyses often take a pragmatic and narrowed approach by focusing simply on the time spent on care. As in formal care, the range of activities included in informal care needs to be clarified, otherwise comparisons between various studies of care are not possible or meaningful. Classification of care into three domains—support in basic ADL, support in IADL, and supervision—provides a useful overview of how informal carers' time is used. The quantity of informal care can be measured in different ways. Direct and continuous timed observation provides clear measures of time spent on informal care, but for practical reasons it is

Panel 6: Formal resources to include in economic assessments of dementia care

- Formal care
- Living situation (at home or in institutions)
- Respite care
- Home social-care visits
- Home medical-care visits
- Home rehabilitation-care visits
- Visits to clinics: physician specialists
- Visits to clinics: general practitioner specialists (or similar)
- Visits to clinics: registered nurses (or similar)
- Visits to clinics: rehabilitation (similar)
- Hospital care (various specialities and departments)
- Day hospital care (eg, day surgery)
- Day care (special care for dementia)
- Day care (not specifically for dementia)
- Use of drugs
- Technical devices and equipment
- Food support (eg, meals on wheels)
- Transport services

useful only in validation and exploration studies.⁴⁹³ Diaries and recall are the most frequently used methods to quantify informal care, although recall might lead to overestimates of caregiver time.⁴⁹⁴

Instruments to assess the amount of dementia care can be generic or specific to a diagnosis. Data can be gathered in different ways—eg, from interviews, diaries, medical records, or registries—but legal and ethical issues, which can vary between and within countries, need to be considered when gaining access to data. In dementia and AD, the Resource Utilization in Dementia (RUD) instrument^{495,496} and the Client Service Receipt Inventory (CSRI)⁴⁹⁷ are comprehensive and frequently used methods to gather data on resource use. When combined with appropriate unit costs, these instruments aim to calculate the costs of dementia care from a societal viewpoint, including the use of health-care and social-care resources and informal-care time. Examples of other instruments are the Caregiver Activities Time Survey (CATS),⁴⁹⁸ the Caregiver Activity Survey (CAS),⁴⁹⁹ and the Resource Use Inventory (RUI).⁵⁰⁰ The CATS captures time use by formal and informal caregivers across a range of tasks and activities, whereas the CAS measures caregiver time and some aspects of caregiver burden. The US RUI, which asks about resource use in the past three months, is designed for AD prevention trials.

How formal-care and informal-care resources are used by people with dementia worldwide is difficult to establish. Data from high-income countries are readily available for the most part, and Alzheimer's Disease International (ADI) and the 10/66 Dementia Research Group, the Alzheimer's Association, and Alzheimer Europe have attempted to broaden the picture to include low-income and middle-income countries. The ADI

For more on Alzheimer's Disease International see <http://www.alz.co.uk/>

For more on Alzheimer Europe see <http://www.alzheimer-europe.org/>

World Alzheimer Report 2010,⁵⁶ and linked publications,^{3,72} were based on a comprehensive review of the use of formal and informal resources worldwide.

Informal care, which was very often deemed to be comprehensive and burdensome (providing all the physical and psychosocial care required by patients), was the most important form of care in low-income and middle-income countries. In low-income countries, the social-care sector (home care, nursing homes, and day care) was almost non-existent, and 90–100% of people with dementia were estimated to live at home (compared with 50–90% in high-income countries). Across all regions, 55–91% of carers were women, although the proportion tended to be lower in high-income regions.⁵⁶ However, the ADI report concluded that the education of women in low-income and middle-income countries, and their increasing participation in the workforce (which should generally be viewed as a positive indicator of human development), tend to reduce their availability for informal caregiving. Spouses were the most common informal caregivers, but this factor varied substantially (eg, daughters or daughters-in-law more frequently serve as caregivers in some countries or cultures). Data for the formal and informal care of people with dementia in eastern Europe are also scarce, but data from Hungary were presented as part of the EuroCoDe project,^{501,502} and similar resource-use figures from Romania were provided as part of the ICTUS study.²⁴ Although few studies have been done (and figures from eastern Europe must therefore be viewed with caution), the contribution of informal care seems to be higher in eastern Europe than in western Europe. Accordingly, the proportions of people with dementia who are living and cared for in nursing homes might be lower in eastern Europe.

End-of-life care

Compassionate end-of-life care should respect social norms (ie, the cultural context in which care is provided). When end-of-life care is provided at home by an informal carer (often a spouse or another family member), perhaps with formal carers available for part of the day, the quality of care will depend on information provision and communication between the patient, family members and those responsible for practical care and important end-of-life decisions. The aim should be to respect the preferences of the patient. The challenges of providing high-quality end-of-life care are discussed in more detail in section 10.

Challenges and future goals

In the absence of effective treatments for dementia, high-quality, person-centred care is essential to meet the health needs of patients and to promote dignity, meaningfulness, and wellbeing as the disease progresses. Two of the main challenges that need to be addressed are how to achieve the vision of timely care,⁵⁰³ and how to ensure the effectiveness and cost-effectiveness of care systems. National strategies for dementia—such as those

in the USA, France, the UK, the Netherlands, Sweden, and many other countries—all emphasise the need for a timely diagnosis.⁵⁰⁴ More generally, these national policy frameworks aim to set out how to improve care and support, including strategies for implementation across health-care, social-care, and other sectors.

For many people with dementia and their families, timely access to care is the main priority. The EU-funded RightTimePlaceCare⁵⁰³ and Access to Timely Formal Care (ACTIFCare) projects show how a timely diagnosis and timely care planning can facilitate care and help patients and their families to take control of their situation. Care that is inadequate or arrives too late is ineffective and can be a burden to some families, whereas too much care too early can create dependency and waste resources. The main arguments for diagnosis at an early stage are linked to care planning for the immediate future (providing appropriate care and support in the short term) and to planning across the life course (working with patients and their carers to prepare for the long-term consequences of the diagnosis).

A timely diagnosis of dementia⁵⁰⁴ is necessary to arrange timely care; however, timely does not necessarily mean as early as possible (such as in a preclinical state) and it does not indicate mass screening programmes, which could lead to false-positive cases.³⁷⁷ Indeed, one enduring challenge in the diagnostic process is accuracy, particularly in the transitions from normal cognition to mild cognitive impairment to very early dementia (section 6). Misdiagnoses can be enormously distressing: a false positive can have negative psychological consequences, whereas a false negative can lead to delayed support and care planning. At present, opportunistic screening for dementia might be a good alternative to mass screening—eg, by offering cognitive testing in a primary health-care centre.⁵⁰⁴ The diagnosis rate of dementia varies within and between countries, but the tip-of-the-iceberg metaphor⁵⁰⁵ seems appropriate. Increasing the rate of diagnosis is not only an issue of resources, but also a question of public awareness and attitudes.¹²

Although care is organised and financed differently across Europe, early detection of dementia and timely access to post-diagnostic support demands the presence of some kind of care infrastructure, including diagnostic resources, support programmes for people living at home, and resources for long-term care in (ideally) home-like institutions with staff available around the clock or as needed. Better understanding is needed about the multidimensional needs and related preferences of people with dementia and their families. Information and advice can help affected individuals to gain some understanding of the disorder and its consequences, and self-directed support—if it is available within a particular national or local context—can empower patients and their families to become active partners in care. The principles of person-centred care, in which the individuality of the person with dementia is acknowledged in all aspects of care and

For more on the ACTIFCare project see <http://actifcare.eu/>

treatment, are essential to improve quality of life for patients and their family members.⁵⁰⁶

The long-term formal care of people with dementia is demanding on staff time and therefore very costly. Long-term care refers not only to institutional provision, but also to (often quite intensive) support in community settings.⁵⁰⁷ Most people with dementia, especially as their condition gets more severe, need support in IADL, basic ADL, and more general supervision, which overall can amount to a much heavier need than that in other chronic disorders in which cognition is not affected.⁵⁰⁸ As the number of people with dementia grows and the funding of long-term care becomes a greater challenge, national governments will be forced to seek new strategies for sustainable long-term care.⁵⁰⁷ However, an obvious tension exists between the need to contain future costs and the desirability to provide better education and training for care staff to improve the quality of care. Offering better working conditions and higher salaries to attract and retain high-quality care staff will push up costs unless that investment in human resources can reduce the risk of expensive admissions into institutions. A Swedish study showed that day care for people with dementia, provided by trained staff, reduced nursing-home admissions.⁵⁰⁹ Formal-care support for family members and informal caregivers—such as day care,⁵¹⁰ respite care,⁵¹¹ counselling,⁵¹² and various case-management programmes^{513,514}—is not only crucial for their quality of life, but can also represent a cost-effective use of resources.

Because most care at home is provided by family members, and in view of the high cost of maintaining current patterns of formal care into the future, efforts are needed to ensure the continued availability of unpaid carers. Recent and expected future demographic, social, and economic trends that have led to smaller families (and hence fewer potential child carers), greater geographical dispersion of families, and higher employment rates for women will add to the challenge of providing informal care for patients with dementia.⁵⁰⁵ In addition to formal-care support, interventions are needed to help informal caregivers to manage the heavy personal burden of caring. Encouraging results have emerged from a support programme in England that offered a coping intervention to family carers of people with dementia: the intervention improved carer mental health and quality of life, and was cost effective.^{516,517} The basic components of support from these studies ought to be reproducible in other country contexts. Counselling programmes can also help to improve the quality of life of informal caregivers and to postpone nursing-home admission.⁵¹²

Policy statements such as those from WHO,^{3,4} the G8 dementia summit,¹⁷³ and the European Parliament⁵ are important for raising the profile of dementia and ensuring that it is high up on the political agenda, and national strategies and local dementia plans are important for turning high-level aspirations into the reality of care and support as experienced by individuals with dementia and

their families. However, despite developments in recent years, research evidence to support the implementation of effective and cost-effective dementia care plans is scarce. More data are needed on the interaction between formal and informal care, on the interactions between different elements of health-care and social-care systems, on the funding challenges of integrated care, and on how best to ascertain and meet the preferences of individuals with dementia and their caregivers.

Summary and recommendations

The care of patients with AD and other dementias does not fit easily into typical health-care delivery systems, especially those that rely on the active involvement of patients. The long-term care of people with dementia often begins at home with a collaborative partnership between informal and formal caregivers. Institutional care for patients with severe dementia is demanding and costly, and little information is available about the transition (eg, in terms of costs and cost-effectiveness) between informal family care and institutional care. Patients' autonomy and ethical considerations (eg, meeting the potentially conflicting needs of patients and their caregivers) are challenges that need to be addressed as part of clinical decision making in dementia care. Worldwide, the burden of care often falls on family members, but effective assisted care and nursing homes with skilled staff will become increasingly important, especially in Europe, with shifting age demographics.

National policy strategies and implementation guidelines for dementia care—with the development of EU or global guidelines as a longer-term aim—are needed in all countries. Such frameworks should address at least the following points.

(1) Timely diagnosis of dementia should be a priority in the planning of care for patients. A timely diagnosis can help to ensure that people with dementia receive the right care at the right time.

(2) Wider availability of evidence-based post-diagnostic support and information programmes—such as counselling, day care, and respite care—is needed for people with dementia and their families and other carers.

(3) The aim of dementia care plans—including informal and formal care—should be to meet not only the basic physical needs of patients, but also the psychosocial and existential needs of people with dementia. Respect for patients' autonomy and acknowledgment of the contributions and needs of informal caregivers are important elements of good dementia care.

(4) Improvements in dementia care will depend on better coordination and communication between health-care, social-care, and other relevant sectors (eg, welfare benefits and housing).

(5) Programmes for case management and coordination need to be developed by different care providers to help people with dementia and their carers to access the services they need, when they need them.

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(6) Local, regional, and national strategies are needed to recruit, educate, train, and retain staff skilled in dementia care.

(7) Action is needed to improve awareness of dementia among health-care and social-care staff, and across society more generally.

(8) Affordable long-term funding plans for dementia care that span health-care, social-care, housing, and other relevant sectors are needed.

Section 10. Ethical considerations

With expanding knowledge of the genetics (section 4) and biology (section 5) of AD, and innovation in the diagnostic and management options for patients (sections 6–9), new ethical issues require careful attention to ensure improved quality of life and wellbeing for this vulnerable group. These issues—which pertain to prevention, diagnosis, guidance in advanced-care decision making, treatment, and policy making—affect both research and care.

The rapidly growing number of people with AD and other dementias is leading to a substantial increase in expected health-care costs. The quest for sustainability in health care—in which health-care expenditures will need to be restricted—gives added urgency to the ethical and societal choices that have to be made for technical and psychosocial advances in dementia care. Here we focus on the ethical issues directly related to patients with pre-symptomatic AD, preclinical or prodromal AD, or AD dementia, their proxies, and the professionals delivering dementia care services (table 14). These issues are drawn mainly from the perspective of Beauchamp and Childress.⁵¹⁸ The principles they set out, which are

internationally accepted as the framework for solving ethical dilemmas in health care, can be summarised as doing good (beneficence), not causing harm (non-maleficence), respecting patient autonomy, and striving for justice for all.

Linking these principles to the widely accepted paradigm of evidence-based medicine results in important messages for policy making. The first is that the introduction of new diagnostic tools should be assessed in terms of proven net benefit for patients, which extends beyond reaching sufficient added diagnostic value to realising the added value of being better informed and providing improvements in wellbeing. The second important message concerns shared decision making and efforts to maximise patient autonomy. Achieving maximum autonomy depends on a sound assessment of the patient's competency to consent, which should be a required skill for all physicians caring for patients at all stages of cognitive impairment. A diagnosis of dementia does not mean that a patient is incompetent, and patient involvement is desirable in all diagnostic and treatment decisions. The third key message is that management of end-of-life care and advance directives should be discussed at an early stage of the disease, irrespective of whether patients live in low-income, middle-income, or high-income countries. These ethical and public health questions could be a greater challenge in low-income countries, where the number of patients with AD is expected to grow most substantially.

Prevention and early diagnosis

As discussed in sections 2 and 3, evidence points to the potential of exercise, nutrition, and other lifestyle

	Patients	Proxies or caregivers	Professionals
Prevention	Are lifelong medication and lifestyle changes beneficial? Should recommendations be targeted to those at risk or extended to the population at large?	What are the effects of early risk assessment (eg, genetic, vascular, AD biomarkers) for dementia with respect to changes in work, family planning, behaviour of relatives, and insurance?	How long, extensive, and rigorous should prevention trials be? How can health-care providers be encouraged to advocate for appropriate changes (eg, lifestyle changes) to their patients?
Pre-dementia diagnosis	Is early biomarker or genetic testing beneficial? Should the whole family be tested genetically? Should a patient participate in prevention trials?	Should a person with a diagnosis of preclinical AD without symptoms be treated as a patient by his or her proxies? Should relatives also be tested for risk factors?	What is the added value of a pre-dementia diagnosis on the basis of biomarkers? How can shared decision making (between patients, family members, and clinicians) about the preferred diagnostic route be realised?
Diagnostic disclosure	What are the pros and cons of knowing vs not knowing the dementia diagnosis? Should truth telling be favoured over paternalistic protectiveness? Is earlier diagnosis beneficial?	Should relatives and other family members be made aware of the diagnosis, especially in the case of prodromal or preclinical AD?	How can advantages and disadvantages of a pre-dementia AD disclosure be balanced? How can stigma associated with an early diagnosis be minimised?
Management	Should a patient participate in drug trials? What should a patient continue to do independently and what should they not do (eg, driving)? How should a patient balance personal vs societal interests?	Should informed consent be given by proxy?	How should competency to consent be assessed?
End-of-life care	How and when should advance directives be realised? Should a patient have an advance directive, restricting use of health services? How active should a patient be in terms of end-of-life planning?	How can autonomy be maximised at home and after admission to an institution? When should active and supportive treatments be stopped? How can caregivers assist in good quality of dying?	How strictly should health-care professionals adhere to advance directives? When should active and supportive treatments be stopped? How can health-care professionals assist in good quality of dying?
Important questions for patients, proxies, and professionals. AD=Alzheimer's disease.			
Table 14: Ethical questions in dementia care			

changes to reduce the risk of AD.⁵¹⁹ Moreover, long-lasting drug trials such as the DIAN study have started to focus on prevention in people at high risk of AD. Several ethical issues need to be considered in the testing and implementation of prevention strategies for AD, including those related to genetic testing, which we addressed in section 4.

In clinical trials, vascular and lifestyle-related risk factors cannot be left untreated in placebo groups because there is already strong evidence that treatment of vascular risk factors and healthy lifestyle are beneficial for the prevention of cardiovascular disease and other health outcomes. In people who do not carry a mutation for autosomal dominant familial AD, dementia risk is the result of interactions between genetic and environmental factors (eg, effects of environmental risk factors are more pronounced in carriers of the *APOE* $\epsilon 4$ allele). Thus, the need for genetic counselling or genetics-tailored guidance as part of dementia risk assessment in trials, and later in clinical practice, needs to be considered.

Another ethical issue is deciding when sufficient evidence exists to start recommending specific prevention strategies, or to start informing and educating the general public about modifiable risk factors. Many potential risk factors cluster in groups with lower socioeconomic status (eg, low education, smoking, obesity, and suboptimum treatment of cardiovascular risk factors), and socioeconomic differences are increasing in many countries. Thus, how these risk groups can be captured by prevention programmes is an important challenge for the future. Importantly, efforts are needed to avoid blaming people with dementia (albeit inadvertently) for having had an unhealthy lifestyle, and to prevent false promises about the benefits of preventive interventions from being reported, especially in the popular media. Results from epidemiological studies are applicable at a population level, but translating them to the individual level is not simple because not all characteristics of an individual can be captured by the average characteristics of a group.

At present, the diagnosis of AD in clinical care is usually made at the dementia stage (section 6). In research studies, however, AD pathology is increasingly detected with the use of biomarkers well before dementia is clinically diagnosed, and even before symptoms of serious cognitive decline occur,⁵²⁰ in line with the proposed NIA-AA^{325–327} and IWG^{328–330} research diagnostic criteria. These criteria cannot be used outside the realm of scientific research at present. Apart from the absence of knowledge about the predictive value of these criteria for the development of clinically overt dementia in an average outpatient population, insufficient evidence exists that early (prodromal) or preclinical diagnosis can improve patients' health and wellbeing.^{521,522}

But the shift to pre-dementia diagnoses in clinical research, and the prospect of identifying at-risk individuals who might benefit from preventive interventions in the future, raise several important

ethical questions. For example, should we inform people that they might be at a high risk of developing dementia when no effective treatment is available? To answer this difficult question, individual benefits need to be weighed against possible disadvantages. Once there is sufficient certainty about a diagnosis of prodromal AD, early disclosure can pave the way for timely psychosocial interventions that can ameliorate symptoms of dementia at more advanced stages, which might be more effective when started early. Early disclosure might also reduce the burden on carers by helping them to adapt to the cognitive and behavioural changes that occur during the natural course of dementia.⁵²³ Moreover, knowledge about the risk of dementia can empower patients and carers to make important decisions about future treatment, care, and life in general (section 9).^{524,525} However, the decision to enter a diagnostic process might be stressful and provoke anxiety, and could be harmful if it raises false expectations of a potential cure.⁵²⁶ Pre-symptomatic diagnosis might also lead to early stigmatisation, and social and emotional isolation, and have important practical consequences for daily life (eg, implications for obtaining insurance or maintaining a driving licence).⁵²⁶

Few empirical data exist on the benefits of early (prodromal) or preclinical diagnosis, and benefits are likely to vary from person to person. People differ in how they cope with perceived cognitive decline, and in their needs and preferences for an early diagnosis. GPs' experience is that many patients do not want an additional diagnostic assessment when they present themselves with cognitive disorders in primary care.⁵²⁵ Memory clinics and Alzheimer's centres are visited by a select group of people, most of whom are highly motivated to receive an early diagnosis and are willing to undergo all diagnostics available.⁵²⁷ Clinicians need to explain clearly which tests add value to the diagnostic process, and which are obtained merely for scientific research. The external validity of results from studies in these selected populations is limited by referral bias. This bias might result in professionals implicitly assuming that this proactive approach represents the preference of all patients with memory complaints, thereby overlooking those who prefer a more conservative approach.

Gauthier⁵²⁶ and Pipersack⁵²⁸ propose a framework for diagnostic disclosure to reduce practice variation and improve average quality of care, which they divide into three phases. In the phase before disclosure, key objectives include determining whether the patient and his or her family members wish to know the diagnosis, identifying the coping style of the patient (defined as the ability to develop adaptive strategies in the face of emotional distress) and the psychological profile of the patient and his or her entourage (ie, carers or companions), and establishing the time and place where the disclosure will take place and the words that will be used to convey the diagnosis and related information.

Important elements for the disclosure phase include establishing what the patient and his or her family know about AD, using terms such as “Alzheimer’s disease” or “memory complaints” instead of “senile dementia”, and avoiding use of words such as “incurable”. The diagnosis should be directed first and foremost to the patient, with the proviso that, should the disease be in its initial stages, the patient’s family should not be informed of the diagnosis without the patient’s consent. Objectives for the phase after the disclosure include ensuring that the information presented is understood by the patient and his or her family members, providing contact information for psycho-education programmes, and scheduling a follow-up meeting.

For the whole process of early, preclinical diagnosis and disclosure with the use of new techniques (eg, imaging and CSF biomarkers), doctor and patient together need to balance the potential benefits and costs before starting the diagnostic process. Before the specialty can reach this point in routine clinical care, new research frameworks for the evaluation of diagnostic tests should be applied, in which the value of a test is measured not only by its diagnostic accuracy, but also by how it affects patients’ health and wellbeing.⁵²⁹ In patient care, a tailor-made approach with shared decision making is the best way to meet the expectations of the patient and his or her family to prevent disappointment about the outcome of a diagnostic work-up and subsequent treatment. This tailored approach is not yet standard clinical practice, and great inter-doctor variability is present. Awareness of the patient’s needs and expectations is a necessary precondition for shared decision making, and appropriate use of decision aids such as evidence-based outcome tables support this shared decision making with patient and family.⁵³⁰ Cultural differences in weighing the principles of doing good, not causing harm, respecting autonomy, and giving all people equal opportunities for good dementia care might lead to different outcomes in shared decision making across countries.⁵³¹

As long as evidence for a net benefit of preclinical diagnosis is lacking, efforts could be made to develop guidance for optimum decision making around pre-dementia (prodromal) diagnoses, taking into account the point of view of all involved (patient, proxies, clinicians, and other professionals). As early diagnosis is introduced into general practice, data should be gathered to understand the effects on quality of care, quality of life, and cost-effectiveness.

Competency to consent

Clinical assessment of competency to consent needs further consideration as more complex decisions have to be made about early diagnostic testing, treatments that are potentially harmful, and genetic testing, which also affects family members. Patients’ competency to consent needs to be addressed when considering options for clinical management and in recruitment for research,

but methods used in these different settings will have to meet different criteria. We focus on the assessment of competency to consent in research, as new ethical questions will be encountered first in experimental contexts. Adequate informed consent is the cornerstone of shared decision making, and because it is now well accepted that a diagnosis of dementia does not mean that a person is, by definition, incompetent to consent, methods are needed to assess capacity to consent on an individual basis. Classically, the following abilities are deemed to be necessary for a judgment of competency: first, ability to receive and understand information; second, ability to process information; third, ability to appreciate the situation and its consequences; fourth, ability to weigh benefits, risk, and alternatives; and fifth, ability to make and communicate a decision.

Several instruments are available for the assessment of competency based on the specific research question that motivated the assessment of capacity to consent, such as the Aid to Capacity Evaluation⁵³² and the MacArthur Competence Assessment Tool (MacCAT).^{533,534} Other instruments are based on vignettes that provide a hypothetical description of a research situation, including elements that are generally thought to be crucial in decision making for dementia treatment, such as whether or not injections should be given or serious adverse events have taken place. Variation in the instruments available to assess competency to consent shows the substantial variation in routine practice in assessments for informed consent. On the one hand, a judgment can be made on capacity to consent in general; on the other, judgment of ability can be made for a specific situation.

Assessment of general decision-making capacity is still often used in clinical practice, although the mental functions needed for competency differ substantially depending on the complexity of the question at stake. Generally, helping the individual to understand specific research information as fully as possible, and checking whether or not they have understood the information (eg, by some standardised questions)—the basis of the MacCAT instrument—are prerequisites for a valid assessment of informed consent. Information should be compatible with the cognitive, visual, and hearing capacities of all patients, including the elderly, and sufficient time should be provided for the information process.

If an individual is judged unable to provide independently informed consent on a specific issue, proxy consent (eg, of a family member) or double consent (of patient and proxy) are good alternatives. However, provision of simplified information for the patient, and asking for verbal consent or assent, are always relevant. Patients’ behaviour should be closely monitored, and in those who demonstrate objection or signs of refusal, any planned procedures should at least be reconsidered. Ultimately, application of the best competency-assessment instrument—which means asking the right

questions to check for competency on specific issues—should be combined with knowledge of the patient's personal hopes, beliefs, and history. Combination of these elements will give physicians and researchers the best chance of arriving at an ethically justified answer on any diagnostic or management questions raised, while maximising the patient's autonomy.

A range of complex issues in genetic testing were introduced in section 4. Participation in research projects can have a major effect not only on the participants themselves, but also on relatives' self-assessment of their health at present and their health prospects for the future.⁵³⁵ At present, relatives do not have a role in the standard individualised informed-consent procedure for patients with dementia in most European countries. However, the question arises as to whether relatives' consent should be required, especially when diagnostic information disclosed as part of a study pertains to the dementia risk of research participants and their family members.⁵³⁶ In the case of clinical genetic diagnostics in the research setting, an investigation of all family members at risk and all patients involved is generally preferred to provide an overview of the familial risk status and the different phenotypes present. Familial investigations of this type should directly involve the family in genetic testing, for which each family member has to give informed consent. If family members do not consent but participating patients do, data collection will be incomplete.

Properly addressing informed consent in people with AD is a routinely required but complex undertaking both in research and in clinical practice, and the optimum approach to informed consent should therefore be an obligatory part of the training for all physicians working with patients with AD. It is the first essential step towards shared decision making, which patients and professionals should try to establish in the face of dementia care dilemmas at each important stage during the disease trajectory.

End-of-life care

When AD or a dementia syndrome due to other causes is the main health problem at the end of life, increasingly complex dementia-specific treatment decisions have to be made in current practice. The increased level of autonomy that most patients and families strive for, together with increased societal awareness of dementia, will probably result in an important increase in ethical, political, and societal dilemmas around end-of-life care for patients with dementia. Patients, family members, and caregivers increasingly play an active part in the weighing of benefits and disadvantages of diagnostic and treatment proposals at the end of life. For physicians, it is increasingly relevant to personalise end-of-life care to do good, cause no harm, and safeguard autonomy as far as possible. Here, we focus on the decision-making process in the use of advance directives, because these directives

could substantially improve the quality of end-of-life care, and are supported by reasonably strong evidence (see appendix for a systematic review of this topic). For the delicate debate on euthanasia and end-of-life care, we refer the reader to other papers.^{537,538}

In advanced-care planning for patients with AD, a key example of what is often debated as appropriate-versus-unnecessary care is the delivery of artificial nutrition and hydration. Decisions on this question are among the most challenging of the various decisions that confront family members and physicians with regard to the medical care of patients with advanced AD.^{526,539} Family members frequently state that non-initiation of such measures would amount to allowing their relative to "starve to death", leaving them with no choice but the placement of a feeding tube. However, the use of feeding tubes has not been shown to prevent or delay death, or to improve functional status, quality of life, or life expectancy, whereas it can cause dysphagia, aspiration pneumonia, and malnutrition.⁵⁴⁰ Despite the existing evidence, many physicians still feel that such measures benefit patients with advanced AD.

Although completion of advance directives at an early stage of the disease is desirable, in the event that advance directives have not been drafted or are incomplete, decision making can be guided by a consensus-based approach that incorporates the patient's preferences, as stated or determined by close family members and others who know the patient well, the wishes of family members, and the opinion of the attending physician.⁵⁴¹ In the event of an impasse in this process, clinical ethics consultants or local clinical ethics committees could provide counsel and assistance. However, in most European countries, these services are not available at present in routine dementia care. Finally, it is imperative that end-of-life decisions, whether guided by advance directives or a consensus-based approach, are based on the principles to minimise harm and to maximise the patient's comfort.

Several international surveys show that most older people consider it relevant and desirable to have information on the health-related scenarios that can be expected in the course of the disease.^{542,543} Advance directives are already widespread and routinely documented as part of hospital and nursing-home admissions. However, most elderly people in the community still do not have an advance directive, even though the benefits in this population—eg, having more control over future hospital care—will probably be the greatest. In older adults, a support service guided by primary-care professionals can lead to a substantial increase in the number of advance directives realised⁵⁴⁴—approaching almost full coverage of older adults in specific regions of the USA, Canada, and Australia with a 10 year tradition of advance-directive support in primary care.⁵⁴⁵

Advance care planning can have a large impact on the care supplied and on the wellbeing and quality of life of

patients and their carers.⁵⁴⁶ For example, the Physician Orders for Life-Sustaining Treatment (POLST) form—which emphasises patients' wishes about the care they receive and is now a legally recognised approach to end-of-life planning in several states in the USA—has a substantial effect on the care provided to older patients, even though advance directives do not always result in care that reflects patients' preferences.^{547,548} As hospital admission is usually stressful and acute or semi-acute, such advance care planning should ideally be implemented proactively in primary care. However, GP support in initiating and completing advance directives is not yet provided routinely as part of primary care in Europe; national support services that educate professionals (appendix) and supply them with evidence-based materials such as information leaflets and clear advance-directive forms might help to remove some of the barriers to the use of advance directives.

In the Netherlands, 5–10% of all elderly people in general practice currently have some form of advance directive or advance care planning.⁵⁴⁸ In older people with advanced dementia and chronic obstructive pulmonary disease or another terminal illness, the number of directives rises to 10–40%.⁵⁴⁹ However, in other European countries and beyond, the figures are probably much lower. In summary, the use of advance directives and advance care planning could be much improved as a crucial step towards better end-of-life management and palliative care in AD. An increase in the use of such directives could improve the quality of care, and reduce the use of limited health-care resources in realising the most appropriate care for patients with dementia.^{550,551}

Summary and recommendations

Ethical considerations are important in dementia risk assessment, treatment, and routine care. The inherent loss of autonomy and competency that coincides with the clinical progression of AD and other dementias is a complicating factor. Ethical considerations can also raise important challenges for the design of clinical trials, especially in large clinical therapeutic trials in which regulatory organisations must work hand-in-hand with academic and industry partners. Bearing in mind the widely accepted framework for solving ethical dilemmas in health care—doing good (beneficence), not causing harm (non-maleficence), respecting patient autonomy, and striving for justice for all—and the need to link these principles to the paradigm of evidence-based medicine, we make the following recommendations.

(1) For early diagnostic procedures in people at very early symptomatic stages, with cognitive complaints or cognitive decline, new research frameworks for the evaluation of diagnostic tests should be applied in which the overall benefits and disadvantages of a new diagnostic test are assessed from both the biomedical and the patients' perspective.

(2) Diagnostic disclosure at all stages of AD should always be based on an accurate diagnosis, and should be well structured, evidence based, and guided by quality indicators and teaching programmes.

(3) Assessment of competency to consent cannot be based on a diagnosis, staging, or neuropsychological testing alone, but requires an individual assessment that is specific for the decision to be made and undertaken with the aim of maximising patients' autonomy.

(4) End-of-life care in dementia can be improved substantially by advance care planning, which can improve wellbeing and quality of life in the latest stages of dementia. The use of advance directives should be discussed and supported as a routine part of primary care.

(5) Increased international collaboration both in research and in dementia care services will demand harmonised ethical standards and will push questions of informed consent and end-of-life decision making to a national or international (EU) level.

G8 targets: towards an international dementia data-sharing network

One of the main targets agreed at the G8 dementia summit is for researchers to work together and share data from their studies, including sharing initiatives for so-called big data (ie, the analysis of large datasets, mostly acquired by online tracking of a large population's behavioural patterns).⁵⁵² However, many obstacles need to be overcome in sharing research and clinical data for dementia research. For example, data sharing demands the safeguarding of relevant privacy and legal issues, the regulation of valid and trustworthy re-analyses, ethical conduct and transparency of conflicts of interest by sponsors, and a guarantee of high-quality research practice for the people who participate in trials and other research. Still, in view of the enormous challenges in the dementia health-care domain, data sharing is the only way to make progress and deliver the promises made by the G8 to our ageing societies.⁵⁵³ Smart use of big data might answer the challenge recognised by the futurist John Naisbitt: “we are drowning in information, but starved for knowledge”.⁵⁵⁴

The promotion of data sharing in the European call for research proposals through the Horizon 2020 programme should be applauded.⁵⁵⁵ However, the EU is steering in the direction of effectively hindering secondary data use by requiring the approval of participants, with increasingly strict privacy legislation that makes no exception for research use.⁵⁵⁶ With regard to dementia research, some points demand specific attention.

Challenges

The first challenge is to establish an international database for longitudinal studies on ageing and dementia, in which the harmonisation of data collection

For more on the Horizon 2020 programme see <https://ec.europa.eu/programmes/horizon2020/>

across all research domains to be covered by the database is sufficiently addressed. As genetic, molecular, imaging, epidemiological, observational, and trial data are all important, this is a huge undertaking. Adequate, standardised description of the data and the characteristics of the setting in which these data are collected (ie, metadata) is crucial but not straightforward.⁵⁵⁵

The second challenge is to safeguard proper informed consent for this broad and gradually extending data application in people who might already have considerable problems with informed consent for the trial in which they participate. Participants' contributions to scientific progress should be facilitated, and they should have a right to innovation⁵⁵⁶—ie, all patients should be able to profit from scientific progress, and be allowed to contribute to research efforts if they want to or be sufficiently protected if they do not.

The third challenge is to organise the quality control and management of such an endeavour.^{557,558} Interests of participating subjects, researchers, pharmaceutical and other companies, universities, research institutes, the general public, and society should be balanced, with transparency about the interests of all parties involved. This overall quality control is a prerequisite for high-quality, reliable research on big data to have the expected impact and value. Interests in the proprietorship of databases and the competitive demand to increase published output might hinder data sharing, and should be tackled with a smart and transparent management structure. The fourth challenge is to make the technical process of sharing data both feasible and safe, for research databases and clinical records.

The way forward

Despite these challenges, the effort is very much worthwhile and should be supported by the G8 and other countries. Data sharing has the potential to trigger changes to public health strategies, to support and improve the preventive strategies that already show promise,⁹³ and to allow breakthroughs in other research areas. These advantages are increasingly recognised throughout scientific communities, prompting 17 major European funders of public health research, coordinated by the Wellcome Trust, to draft a joint statement supporting public data repositories.⁵⁵⁷ Importantly, the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study has shown that large-scale data sharing is possible and, if done to the highest possible research standards with careful pre-planning, can be highly successful.⁵⁵⁹

Lessons have been learned from the Dutch National Care for the Elderly Programme in the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS) initiative, a national data-sharing project that encompasses 64 research studies in elderly care.⁵⁶⁰ To comply with data protection legislation, external users will be able to access a fully anonymised database only.⁵⁶¹

To circumvent issues related to publication rights and to prevent uses of the data for which they are unsuitable, selected members of the research consortium will assess all applications for secondary use for scientific feasibility and overlap with studies that are already planned or in progress. Rather than erecting barriers to secondary use, this brief assessment aims to improve secondary use because the goal is to identify potential synergies with studies that are already underway to connect applicants with researchers focusing on the topic, and to optimise the methodology of a proposed study to the possibilities offered by TOPICS-MDS. To further protect the interests of external users, to guarantee the involvement of patient representatives, and to improve the societal relevance of requests, a societal board has been established, which acts as a safeguard against preferential release of data and evaluates the societal relevance of proposals.

International data sharing in dementia research is challenging, but recent examples show that it is possible. However, the development of overarching research databases takes time, money, effort, and expertise. The establishment of an international dementia research network would help to support the exchange of best practices and experiences, and to produce international consensus guidelines on the subject. As the G8 countries underlined the importance of data sharing in dementia, a commitment to support financially and organise such a unique international dementia data-sharing network sets the framework for the ambitious goal of finding a cure within 15 years.

Conclusion and future European perspectives

AD is the leading cause of dementia, and because the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically as life expectancy increases worldwide. The explosion in care costs and associated societal burdens of AD and other dementias threatens to become overwhelming, even in resource-rich countries. However, AD is not an inevitable consequence of ageing, and further work is needed to identify modifiable risk factors and protective factors—including a range of lifestyle factors—that could form the basis of effective, feasible preventive interventions. Although no cure for AD exists and no therapeutic option is available to delay the inevitable progression of the disease, an emphasis on early detection and integrated, team-oriented, evidence-based care—with a focus on the physical, psychosocial, and existential health needs of the patient and support for informal caregivers—has the potential to improve the quality of life of patients and their families.

The pharmaceutical industry and government-sponsored research programmes, in partnership with multinational academic consortiums, have advanced several promising therapeutic leads but, overall, progress in the development of effective treatments for AD has so far been disappointing. Nonetheless, basic biomedical

For more on the ADNI study see <http://www.adni-info.org/>

For more on the TOPICS-MDS initiative see <http://topics-mds.eu/>

science has provided important insights into the genetics and biology of AD, and knowledge about the causes and pathological mechanisms of the disease could ultimately lead to the identification of new, valid therapeutic targets and the development of a cure.

AD research with human participants is extremely complex and expensive, partly because of the limitations of study design (eg, non-optimum outcome instruments), the absence of accessible biomarkers at early stages of the disease, and ethical considerations. Moreover, drug-development programmes now pose an unacceptably high financial risk to investors. But in the absence of a cure for AD and in view of the increasing financial and societal burden of dementia, policy makers and governments have a powerful incentive to provide more resources to develop therapeutics. Even minor advances to delay progression or ameliorate symptoms might have substantial financial and societal benefits. At present, several factors in Europe constitute bottlenecks to progress in basic, translational, and clinical AD research:

(1) Investment, funding, and human resources: in Europe, investment in AD research is low compared with that in the rest of the world and for other diseases.

(2) Fragmentation and poor coordination of research efforts: in Europe, research policy is set by the European Commission and by the 28 member states at a national level, whereas cooperation and collaboration are needed.

(3) Knowledge application: Europe must support innovation and introduce new methods and processes for promoting the application of research results in clinical practice.

(4) Research infrastructure: European research infrastructures should be strengthened—eg, with standardised imaging capacities, CSF analyses, biobanks, and databases to achieve more reliable data.

(5) Improvements are needed to help researchers build careers in Europe, with full freedom of movement within the EU.

Although much more basic biomedical research will be required to understand the biology of dementia, there is a clear need to develop and implement new approaches for pharmaceutical research and development to target AD and other dementias. In the context of current knowledge and available resources, no individual pharmaceutical company (or even an alliance of companies) is likely to be able to develop an effective therapy. Large clinical trials of drug candidates will continue to be extremely expensive and complex to plan and administer, and no clear strategy exists to mitigate risk when an emphasis on shareholder return predominates. Therefore, we advocate the formation of public-private partnerships in which large consortiums of pharmaceutical companies and public governmental agencies can deploy capital resources and share risk.

An alliance of EU health research agencies, in partnership with the pharmaceutical industry, will be

able to assemble the required expertise and provide the capital necessary to initiate and advance large-scale programmes of drug discovery and development. Essentially all major clinical-trial initiatives in progress that target early-onset or familial dementia syndromes are USA led, with at least partial NIH support. A complementary European strategy could be extremely productive—perhaps to target sporadic cases in which the onset of symptoms occurs at older average ages. Such a strategy might be most effective with several therapeutic approaches tried in parallel, rather than the typical approach of successive linear trials with long individual timelines.

At the same time, a public health perspective should be systematised and viewed as a core principle in efforts to defeat AD and other dementias, rather than playing second fiddle to the search for a magic-bullet therapy. Would controlling known risk factors decrease the incidence or severity of AD? Do elderly people with normal cognition and mental function harbour protective factors such as antibodies against amyloid protofibrils? These types of questions can be addressed only through complex epidemiological studies, perhaps in combination with diagnostic testing in the setting of sophisticated public health networks. The infrastructure for such studies might already exist within the EU, and should be exploited to provide solid data that might lead to new approaches to mitigate disease or provide new targets for therapy.

In an environment of increased pressure to reduce public spending, options should be debated in an open forum with a well informed public constituency so that long-term strategic support can be assured. The funding of translational research, drug discovery, and patient-oriented clinical trials will need to extend beyond the time horizon of any individual political campaign, and the public should understand that long-term commitment is necessary. It is likely that treatment of dementia syndromes will become multidimensional, with combinations of treatments for a specific diagnosis, or several treatment options that depend on a particular molecular or genetic diagnosis. As an example, cancer treatment is now often patient-specific and cancer is no longer thought of as a single entity, but rather as a complex multifactorial constellation of disease, often with acute and chronic phases. Oncology centres have evolved to become clinical research enterprises where gene sequencing can be part of routine care. The future of dementia treatment might be similar, and will require systematic public investment to focus scientific biomedical resources, while not depleting basic clinical care and support. Dementia syndromes are insidious, progressive, and chronic, and the importance of evidence-based care and support cannot be over emphasised. Even quite low-cost innovations and interventions could have a huge effect on the quality of life of patients and their families and caregivers.

The science of disease biomarkers in AD and related dementias is still in its infancy. The discovery of informative biomarkers should be a priority. New biomarkers and diagnostic strategies to detect synaptic loss and apoptotic cell death in the central nervous system are urgently needed. The search for biomarkers could take place in large cohorts of patients, even independently of therapeutic options. At present, in most countries, payment for expensive diagnostic services is linked to the potential for treatment. For example, a diagnostic PET scan might not be indicated because the results would not be used to direct therapy, but more widespread use of advanced diagnostics—especially in the setting of the collection of metadata, including blood, CSF, and genetic analyses plus advanced memory, cognitive, and behavioural testing—might lead to better understanding of the natural history of disease and the stratification of dementia syndromes for the purposes of effective therapeutic trials. Of course, the ethical concerns about clinical-trial design for diagnostic and therapeutic modalities are paramount when informed consent cannot be readily or reliably obtained from participants, at least at more advanced stages of disease.

In summary, the use of effective strategies to prevent or cure AD and other dementias will demand an urgent reassessment of traditional paradigms of health-care practice. Although basic biomedical research initiated by individual investigators can lead to breakthroughs and important discoveries, and the pharmaceutical industry has had an unparalleled series of successes over many decades, a disease threat as large and complex as AD in an ageing population cannot be left to the fortunes of unfocused research programmes on the one hand, or to the whims of corporate risk–return business analysis on the other. A public–private partnership on a multinational scale is needed, and the EU is well positioned—in view of its excellent health-care delivery system, basic single-payer model, outstanding research infrastructure, and strong pharmaceutical industry base—to take the world lead, in partnership with international organisations, to develop new approaches to prevent or cure AD and other dementias and to provide models of compassionate care for patients with dementia.

Contributors

BW chaired the *Lancet Neurology* Commission. Together with GJ, AC-M, and TPS, he oversaw the collation of sections and did the final general editing of the paper. BW, GJ, and AW wrote the introduction. The executive summary was written by TPS, BW, GJ, and AC-M. Lead author for section 1 was LJ; AW and MKn contributed to the organisation, writing, and editing of the section. Lead authors for section 2 were LF and CQ, who contributed equally to the work; SA, CBr, and JG participated in the development, writing, and editing of the section, and HZ wrote the subsection “Traumatic brain injury and dementia”. Lead authors for section 3 were MKi and FM, who contributed equally to the work; SA, HF, LSS, and BW contributed to the writing and editing of the section, and AW wrote the subsection “Health economics of dementia prevention”. Lead author for section 4 was CG; CG and PA contributed equally to the section. Lead author for section 5 was AC-M; TPS, KI, LOT, and FJ contributed to the section. Lead author for section 6 was FJ; PS, GW, CBr, and AC-M contributed

to the section, and CG wrote the subsection “Post-mortem diagnosis of AD”. AN was lead author of the subsection “Use of biomarkers in AD diagnosis”, with contributions from HZ (CSF biomarkers), BD, RS, GBF, and LOT. Lead author for section 7 was LSS; AC-M, BW, HB, HF, and MKi contributed to the section, and FM compiled tables 11–13. Lead author for section 8 was CBr; MKi, HB, DE, and SG contributed to the section. Lead author for section 9 was AW; DE, LJ, JG, SG, GW, and MKn contributed to the section. Lead author for section 10 and the systematic review of advance directives (appendix) was MOR; HB and SG contributed equally to the section. The section “G8 targets: towards an international dementia data-sharing network” was written by MOR and RM, who contributed equally to the work. The concluding section was written by TPS, BW, GJ, and AC-M.

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BAILES

EXHIBIT 13

The phenotypic variability of amyotrophic lateral sclerosis

Bart Swinnen and Wim Robberecht

Abstract | Classic textbook neurology teaches that amyotrophic lateral sclerosis (ALS) is a degenerative disease that selectively affects upper and lower motor neurons and is fatal 3–5 years after onset—a description which suggests that the clinical presentation of ALS is very homogenous. However, clinical and postmortem observations, as well as genetic studies, demonstrate that there is considerable variability in the phenotypic expression of ALS. Here, we review the phenotypic variability of ALS and how it is reflected in familial and sporadic ALS, in the degree of upper and lower motor neuron involvement, in motor and extramotor involvement, and in the spectrum of ALS and frontotemporal dementia. Furthermore, we discuss some unusual clinical characteristics regarding presentation, age at onset and disease progression. Finally, we address the importance of this variability for understanding the pathogenesis of ALS and for the development of therapeutic strategies.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a heterogeneous disorder. The genetic heterogeneity is obvious, given the long list of genes in which mutations cause ALS.¹ Considering that the aetiology of ALS remains unknown in nearly 90% of cases, the true causal heterogeneity is likely to be even larger. The mechanistic heterogeneity of ALS adds to the complexity of this disorder.² The fact that ALS starts in the bulbar region in some patients, and in the limbs in others, has always been evident to clinicians, and is often used as stratification parameter in clinical trials. Phenotypic variability goes far beyond the site of onset, however, and can be observed with regard to age at onset, familial occurrence, type of motor neuron involvement, extent of extramotor involvement, and disease duration, among other parameters. Here, we will review several aspects of this phenotypic heterogeneity of ALS and discuss some of its implications.

A student's vignette: classic ALS

Variability in location of onset

Spinal onset

In most patients, ALS starts around the age of 60 years with asymmetric, painless weakness in a limb, referred to as spinal-onset ALS (Figure 1).^{3,4} Clinical examination usually reveals atrophy and weakness of muscles, fasciculations, hyperreflexia (or at least brisk reflexes), and often a mild to severe hypertonia.³ Clinicians designate weakness, muscle atrophy and fasciculations as lower motor neuron signs, whereas hyperreflexia and hypertonia indicate upper motor neuron involvement (Figure 2). Interestingly, the Babinski sign—also known as the extensor plantar reflex—is often absent, and

hypertonia is often 'glue-like', reminiscent of what one finds in frontal or even extrapyramidal syndromes, and different from the clasp-knife phenomenon of the upper limbs in stroke and the spastic kick of the lower limbs in familial spastic paraparesis. Initially, the abnormal findings can be patchy, but the disorder spreads relentlessly over time. In many but not all patients, this spread seems contiguous, a phenomenon hypothesized by some authors to reflect the spread at the cellular level.⁵

Bulbar onset

In about 20% of patients with ALS, the weakness starts in bulbar muscles, with dysarthria, dysphagia and tongue fasciculations (Figure 2).^{3,6} A brisk jaw jerk is often found in these patients, and pseudobulbar affect (an inaccurate term mainly referring to uncontrolled crying or laughing) is sometimes present. The presence of limb hyperreflexia suggests that the disease has already spread. Bulbar-onset ALS was originally considered to be a different disease from ALS, and was termed 'progressive bulbar palsy'.⁷

The onset of symptoms is gradual in most patients, but some become aware of their problems quite abruptly; neurologists often need to consider stroke and myasthenia in the differential diagnosis of these patients. Bulbar-onset ALS must also be distinguished from Kennedy's disease (bulbar and spinal muscular atrophy) or from Brown–Vialeto–Van Laere syndrome (see below).³

Patients with bulbar-onset ALS have a worse prognosis than patients with spinal onset, with a mean survival of 2 years and long-term (>10 years) survival of only 3%.⁶ The poor prognosis is mostly attributable to the fact that patients with bulbar-onset ALS are prone to aspiration and nutritional problems, and is possibly also related to earlier respiratory dysfunction due to involvement of the cervical

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Competing interests

The authors declare no competing interests.

REVIEWS

Key points

- Amyotrophic lateral sclerosis (ALS) is a highly heterogeneous entity
- Cognitive impairment is a common feature of ALS: frontotemporal dementia and ALS constitute the ends of a spectrum reflecting different manifestations of the same pathogenic mechanism
- Upper and lower motor neuron involvement is variable in ALS, and yields a spectrum with primary lateral sclerosis and progressive muscular atrophy at the two ends
- In rare cases, extrapyramidal, cerebellar, sensory and autonomic systems can be affected in ALS, indicating that ALS should be seen as a multisystem neurodegenerative disease
- The method and timing of assessment of a patient account for a considerable proportion of the clinical variability
- The biology underlying the ALS phenotype needs to be elucidated, as the pathophysiological mechanisms of the disease could be targets for therapeutic interventions

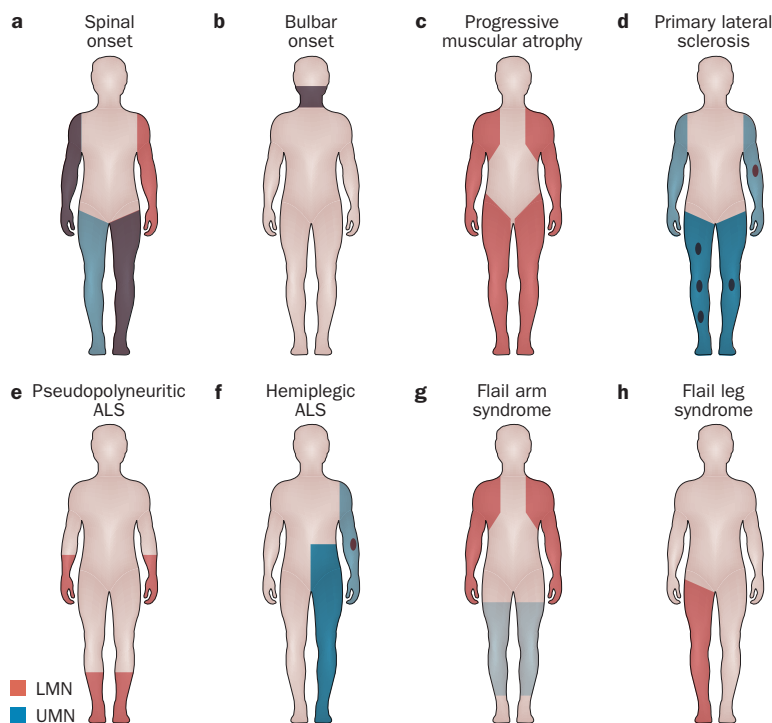


Figure 1 | Pattern of motor involvement in different ALS phenotypes. Red indicates LMN involvement, blue indicates UMN involvement. Darker shading indicates more severe involvement. **a** | In spinal-onset ALS, patchy UMN and LMN involvement is observed in all limbs. **b** | In bulbar-onset ALS, UMN and LMN involvement is observed in the bulbar muscles. **c** | In progressive muscular atrophy, LMNs in arms and legs are involved, often proximally. **d** | In primary lateral sclerosis, UMN of arms and legs are primarily involved, but later in the disease, discrete LMN involvement can be detected. **e** | In pseudopolyneuritic ALS, only LMNs restricted to the distal limbs are involved. **f** | In hemiplegic ALS, unilateral UMN involvement with sparing of the face, and sometimes discrete LMN involvement, can be observed. **g** | In flail arm syndrome, LMN involvement is restricted to the upper limbs, but mild UMN signs can be detected in the legs. **h** | In flail leg syndrome, LMN involvement is restricted to the lower limbs, and is often asymmetric. Abbreviations: ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron; UMN, upper motor neuron.

phrenic motor neurons.⁸ Loss of ambulation is an ominous sign for these patients, indicating mean life expectancy of only 3 months.⁹ The site of onset is, therefore, used as a stratification parameter in clinical trials.

Respiratory onset

In about 3–5% of patients, ALS is characterized by respiratory onset, with orthopnoea or dyspnoea, and mild or even absent spinal or bulbar signs.⁶ Respiratory-onset ALS has a male predominance.^{6,10} The prognosis is notoriously poor, with a mean survival of 1.4 years and no long-term survival.^{6,10}

Genes and type of onset

The factors that determine the nature of ALS onset remain unknown. Sex hormones are suspected to contribute to the type of onset because of the striking female predominance in bulbar-onset patients.⁹ Bulbar onset is very frequent in ALS associated with *C9orf72* mutations; by contrast, ALS associated with mutations in superoxide dismutase 1 (*SOD1*) almost never starts in the bulbar motor neurons (see below). Such associations between the type of onset and genetic causes suggest that the site of onset is unlikely to merely reflect a stochastic process.

Familial versus sporadic ALS

About 10% of patients with ALS have an affected relative and are, thus, considered to have familial ALS.¹ Those who do not have an affected relative are considered to have sporadic ALS. It is likely that many if not all cases of familial ALS will turn out to be hereditary in nature, because in a growing number of the pedigrees of patients with familial ALS, a causal mutation is eventually identified. In some populations, such a hereditary cause is identifiable in nearly 80% of familial ALS cases.¹ Mutations in *SOD1*, *TARDBP* (the gene that encodes TAR DNA-binding protein 43 [TDP-43]), *FUS* and *C9orf72* explain more than half of cases of familial ALS.¹

The cause of sporadic ALS is unknown, but twin studies suggest that it has a genetic component as well, possibly in interaction with as yet unknown environmental factors.¹¹ Some patients with sporadic ALS initially receive a wrong classification, as they are later found to have a hereditary form of the disease when they are found to carry a causal mutation. Reduced penetrance and a low number of offspring are the main explanations for the misclassifications,¹³ but other contributory factors include a lack of complete information of the medical history of the patients' relatives, non-paternity events, and variability of the phenotypic expression.¹⁴ In most populations, nearly 10% of the patients with so-called sporadic ALS carry a *C9orf72* mutation;¹ the advanced age at which *C9orf72*-associated ALS often begins and unexpected variability of the phenotype associated with *C9orf72* mutations (see below) are the main reasons why these patients are misclassified.

Age at onset

Although ALS usually starts in the fifth or sixth decade of life, onset at almost any age has been described. Juvenile ALS is defined as ALS with age at onset before 25 years, and the course of progression is generally slower than in other forms of ALS.^{15,16} Mutations in *ALS2*, *SETX* and *FUS* are well-known causes of juvenile ALS.^{1,14} Patients carrying the *FUS* Pro525Leu mutation have a notoriously

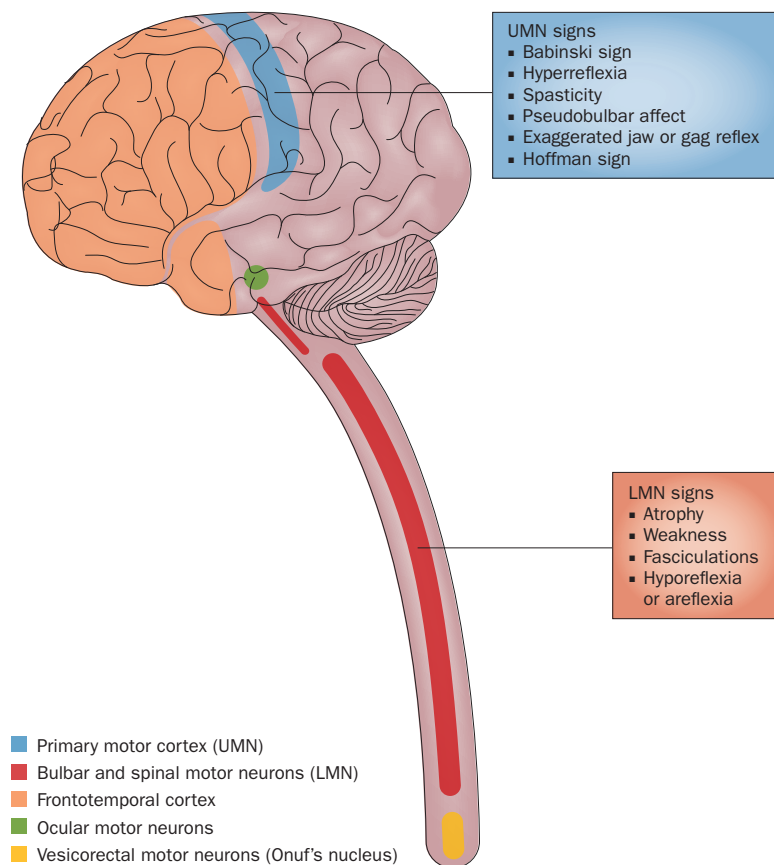


Figure 2 | Preferential sites of neuronal involvement in ALS. UMNs in the primary motor cortex (blue) and bulbosplinal LMNs (red) are the preferentially affected sites in ALS. Neurons in the frontotemporal cortex (orange), however, are frequently involved as well; the resulting phenotype will be in the frontotemporal dementia–ALS spectrum. Ocular (green) and vesicorectal (yellow) motor neuron involvement is rare, and happens mostly in cases of longstanding disease. Abbreviations: ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron; UMN, upper motor neuron.

poor prognosis.^{17–19} In some forms of ALS, such as the *SETX*-associated ALS type 4, the phenotype is so atypical that some authors suggest they should be considered as separate disease entities rather than ALS.^{20,21}

60% of patients with disease onset between 20 and 40 years of age have predominantly upper motor neuron involvement, and relatively few of these patients (15%) have bulbar-onset disease.¹⁵ Older age at onset is associated with decreased likelihood of upper motor neuron involvement (20%), increased probability of bulbar onset (some studies report up to 50% with onset after 80 years of age), and poor prognosis.^{9,22,23} Onset after 80 years is associated with a particularly short survival.¹⁶

Rate of progression

Although median survival in ALS is generally around 3 years from diagnosis, variability in survival is remarkable and reflects the variability in the rate of disease progression. The difference in individual rates of functional decline, even in small series of patients, demonstrates this high variability (Figure 3), and is one of the factors that complicate clinical trials in ALS.

At one end of this continuum are the 10% of patients who live longer than 10 years with ALS.¹⁶ At autopsy, their disease does not differ from classic ALS.²⁴ Long survival is seen more frequently in patients with juvenile ALS and upper motor neuron-predominant ALS.^{16,23} Some forms of hereditary ALS are known to be associated with particularly long or short survival. For example, long survival has been reported in association with the *SOD1* Asp90Ala mutation, whereas the *SOD1* Ala4Val mutation can induce a very aggressive disease.¹ Patients with a hexanucleotide (GGGGCC) expansion mutation in the *C9orf72* gene have shorter survival than the average ALS patient.^{25–28}

Even within families in which members carry the same mutation, variability in progression rates is large.^{29–31} This finding suggests that there is no straightforward relationship between the genetic cause and phenotype but, rather, that factors—either genetic or environmental—modify the phenotypic expression, and in particular age at onset and disease progression. It is important to identify these modifying factors, as they could be targets for therapeutic intervention, even in the absence of knowledge of the cause of disease. Delaying age at onset or attenuating progression rate and, thus, functional decline is of obvious therapeutic interest. Several small animal models, such as *Drosophila* and zebrafish, have been used to screen for such modifiers, resulting in the identification of ‘druggable’ targets or even novel causes of ALS.²

Motor neuron involvement

Lower motor neuron dominance

Evidence of both upper and lower motor neuron involvement is required for the diagnosis of ALS, and has been incorporated in the so-called El Escorial criteria.³² Of note, however, these criteria were developed to reduce the phenotypic variability in clinical trials, and were not intended for clinical decision-making.

Assessing the involvement of upper motor neurons relies on clinical judgement—largely, evaluation of the briskness of deep tendon reflexes. Neurologists sometimes disagree on the interpretation of this measure: some consider a preserved reflex in an otherwise atrophic muscle to be a sign of upper motor neuron involvement, while others require the reflex to be hyperactive to reach the same conclusion. A patient can, thus, be considered to have ALS by one clinician, and to have progressive muscular atrophy (PMA) by another (Figures 2 and 4).

Progressive muscular atrophy

PMA refers to an adult-onset lower motor neuron disorder that differs from the rare instances of adult-onset spinal muscular atrophy (SMA) in several respects: PMA is usually asymmetric, can have distal and/or proximal onset, and progresses much faster than SMA.³ Thus, PMA essentially equals ALS minus (convincing) upper motor neuron findings. PMA is believed to constitute about 5% of all patients with motor neuron disease (MND).³³ The question arises as to whether PMA and ALS have different pathophysiological backgrounds and thereby represent different disorders, or whether PMA represents the end of a spectrum of lower versus

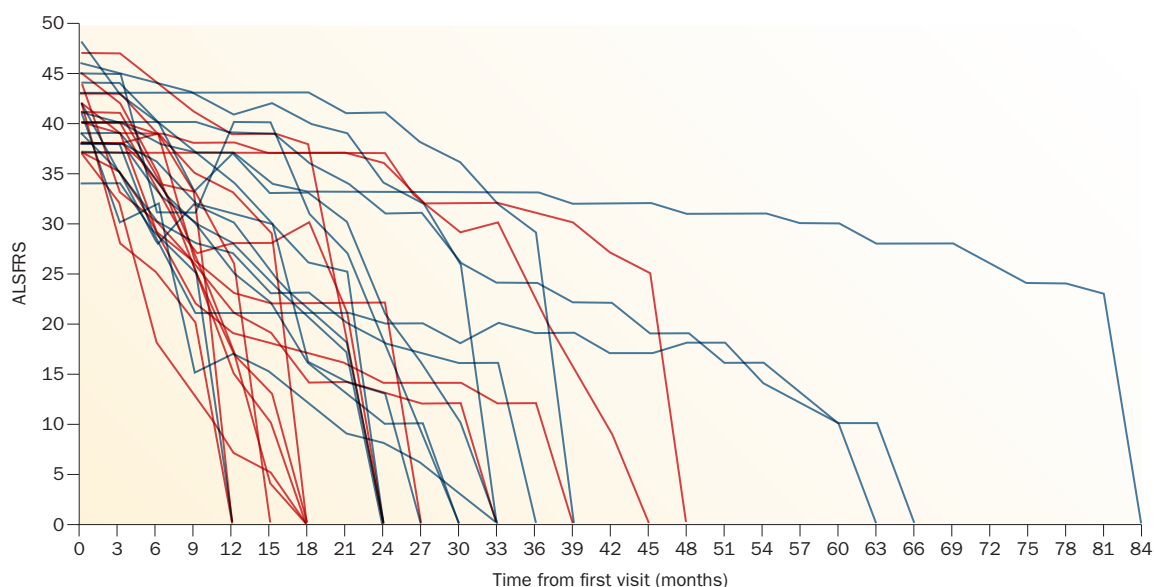


Figure 3 | Variability of disease progression in ALS. ALSFRS scores of 30 randomly selected patients (Leuven University Hospital, Belgium) with ALS, from first visit to death. Patients with bulbar-onset disease are indicated in red, patients with spinal-onset disease are indicated in blue. Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS, ALS Functional Rating Scale.

upper motor neuron involvement (Figure 4). Support for the latter hypothesis comes from the finding that some *SOD1* mutations give rise to a syndrome that primarily affects lower motor neurons: patients with the *SOD1* Ala4Val mutation are classified as having ALS, but they lack upper motor neuron involvement.^{34,35} Furthermore, imaging studies have shown widespread, progressive frontal abnormalities in PMA that are similar to those in ALS,^{36,37} and postmortem studies of patients with lower motor neuron signs only often show classic lateral spinal cord involvement.³⁸ Patients with PMA fare slightly better than those with clinical evidence of both lower and upper motor neuron involvement (see below).

Flail arm syndrome

Some patients have lower motor neuron involvement that remains limited to the upper limbs for at least 12 months (Figure 2). These limbs are often non-functional, while the lower limbs remain normal, although hyperreflexia and some hypertonia may be present.^{39,40} This variant is called flail arm syndrome (also referred to as the scapulohumeral form of ALS, Vulpian–Bernart syndrome, hanging arm syndrome, neurogenic man-in-a-barrel syndrome or brachial amyotrophic diplegia), and has a striking male predominance, with a male:female ratio of 4:1.^{40,41} After about 20 months, almost all patients with this syndrome develop more-widespread disease; the prognosis is somewhat better than that of classic ALS, with mean survival of 4 years and long-term survival of 17%.⁶

Flail leg syndrome and dropped head syndrome

Even less frequent than flail arm syndrome is flail leg syndrome, characterized by often asymmetric, and primarily distal, lower motor neuron involvement in the lower limbs for at least 12 months.⁴¹ Subtle upper motor neuron signs usually emerge over time,^{41,42} and after a

mean of 16 months, the upper limbs and bulbar region also become affected.⁶ Progression is slightly slower than in classic ALS.^{6,41,42} Flail leg syndrome with mainly distal and bilateral involvement is also referred to as the ‘pseudopolyneuritic’, ‘Marie–Patrikios’ or ‘peroneal’ form of ALS.^{41,42}

Equally rare is onset in the cervical region, limited to the extensors of the neck, resulting in dropped head syndrome.⁴³ Such clinical presentation needs to be differentiated from myasthenia gravis or a (typically inflammatory) myopathy.

Upper motor neuron dominance

Some patients present with upper motor neuron findings only and, therefore, do not meet the standard criteria for ALS. These patients are considered to have primary lateral sclerosis (PLS); however, most of these individuals gradually develop lower motor neuron involvement.^{44,45} The diagnosis of PLS can, therefore, only be made after a sufficiently long period of observation, as 23% of those who eventually develop lower motor neuron signs do so only after 4 years.⁴⁴

PLS constitutes about 5% of all cases of MND.⁴⁶ This condition is characterized by slower progression, more-prolonged retention of functionality, sparing of respiratory function and less-severe weight loss than seen in ALS.⁴⁷ Even in patients with PLS, lower motor neuron involvement is often evident at autopsy,⁴⁶ which, together with the fact that known ALS-causing mutations can present with upper motor neuron involvement only,¹ suggests that PLS could be considered to be at one end of a spectrum of upper motor neuron involvement, with PMA being at the other end (Figure 4).

Interestingly, upper motor neuron involvement can be strikingly asymmetric. An extreme form is the unusual hemiplegic variant also called Mills syndrome or

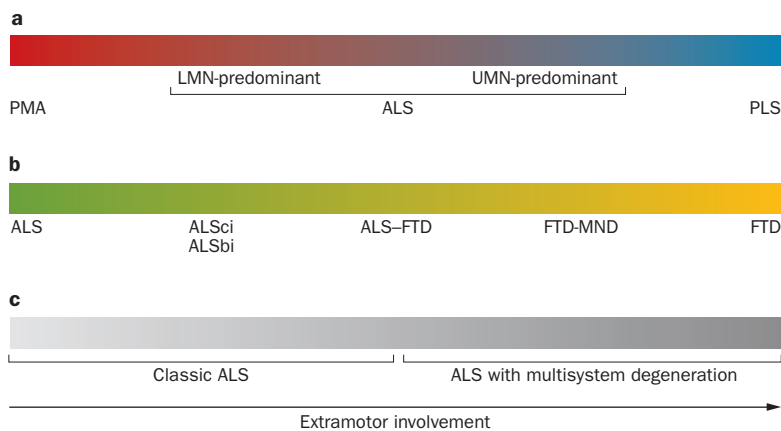


Figure 4 | ALS, a spectrum disorder. **a** | PMA (isolated LMN involvement) and PLS (isolated UMN involvement) constitute the ends of a spectrum of LMN and UMN involvement; intermediate phenotypes are considered to be different expressions of ALS. **b** | ALS and FTD constitute the ends of a spectrum of motor neuron and frontotemporal neuron involvement. This spectrum includes patients with ALS who express isolated ALSci or ALSbi, and patients with ALS who meet the Neary criteria for FTD and are, thus, diagnosed with ALS-FTD. Some patients with FTD have insufficient motor neuron involvement for a diagnosis of ALS, and are classified as FTD-MND. **c** | A spectrum of extramotor involvement is possible in ALS, ranging from classic ALS with no to mild extramotor involvement to ALS with extrapyramidal, cerebellar, sensory, autonomic, urinary or oculomotor involvement, designated as 'ALS with multisystem degeneration'. Abbreviations: ALS, amyotrophic lateral sclerosis; ALSbi, ALS with behavioural impairment; ALSci, ALS with cognitive impairment; FTD, frontotemporal dementia; LMN, lower motor neuron; MND, motor neuron disease; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; UMN, upper motor neuron.

progressive hemiplegia.^{48,49} This form usually begins with unilateral upper motor neuron involvement in the lower limb, followed by slowly progressive ipsilateral involvement of the arm, with relative sparing of the face. After a variable time period, the disease spreads to the initially unaffected side.

To conclude, several lines of evidence suggest that ALS, PMA and PLS are expressions of one biological entity: patients in the same family, or patients carrying mutations in the same ALS-associated allele, can have classic ALS, PMA or PLS; the clinical characteristics of a patient can vary over time; and detection of upper and lower motor neuron involvement depends on the method of assessment. The main reason for distinguishing these phenotypes is the difference in prognosis. Patients with isolated lower motor neuron involvement live only slightly longer than patients with clinical evidence of both upper and lower motor neuron involvement,^{50,51} whereas patients with PLS, on average, live longer than those with ALS.⁴⁷ The mean survival of ALS patients with predominant upper motor neuron signs—6 years, with about 30% of cases exhibiting long-term (>10 years) survival—lies between that of PLS and classic ALS.^{6,44} This difference may simply reflect the biological burden of disease (Figure 5). It also implies that the best approach is to study patients with both lower and upper motor neuron involvement only if one intends to (prognostically) homogenize a study population, as is needed, for example, in clinical trials that investigate the effects of a drug on function or survival.

Nonmotor involvement in ALS

ALS has long been believed to be a neurodegenerative disorder with isolated motor neuron involvement. Absence of cognitive deterioration was initially even postulated as a prerequisite for a diagnosis of ALS. Nowadays, however, it is evident that other neurological systems can be affected, with cognitive impairment being the most frequent manifestation of nonmotor involvement.

Cognitive impairment

Over the past few decades, a spectrum of cognitive involvement has been increasingly acknowledged as a part of ALS.^{52–54} Degenerative changes in layer V of the frontotemporal lobe represent the anatomical substrate of this cognitive decline, hence the name frontotemporal lobar degeneration (FTLD). Up to 25% of patients with ALS meet all criteria for the clinical manifestation of FTLD, frontotemporal dementia (FTD), mostly of the behavioural variant.^{55,56} Mild to moderate frontal dysfunction or language abnormalities are even more frequent, but can escape routine clinical examination and be detected on detailed testing only. Apathy (seen in 60% of patients), disinhibition, delusions and stereotypic behaviour are the most frequently encountered behavioural changes.^{52,55} Whether depression (reported in up to 75% of patients⁵⁷) can also be attributed to the ALS pathology is difficult to judge, as patients have obvious reasons for reactive depression. It should be kept in mind that even mild frontal impairment can contribute to non-compliance with percutaneous endoscopic gastrostomy therapy and non-invasive ventilation, difficulties handling communication machines, psychosocial problems and decision-making, and undoubtedly increases caregiver burden.^{52,53}

ALS-FTD spectrum

ALS is now accepted to constitute a continuum with FTD. Pure ALS (without any evident cognitive abnormality) and pure FTD (without any obvious motor abnormality) are located at the opposite ends of this spectrum (Figure 4). ALS patients with mild behavioural dysfunction are classified as having ALS with behavioural impairment (ALSbi),⁵² whereas patients with mild executive and language dysfunction are said to have ALS with cognitive impairment (ALSci).⁵² Patients with ALS who meet the Neary criteria for FTD are considered to have ALS-FTD. Of note, up to 50% of patients with a diagnosis of FTD have some motor neuron involvement (which may go unnoticed by the patient), and are said to have 'FTD-MND'.^{52,54}

In ALS, the onset of cognitive problems usually precedes that of motor dysfunction.^{53,54} Frontotemporal involvement can only become evident in retrospect, when motor problems bring the patient under medical attention. Interestingly, eye movement disorders, probably related to frontal network dysfunction, are especially prevalent in these patients.⁵²

The prognosis of patients with subtle cognitive impairment is similar to that in classic ALS,⁵⁵ but patients with ALSbi or ALS-FTD have a worse prognosis than do patients with ALS alone.⁵³ The life expectancy in ALS-FTD is 2.4 years from disease onset, approximately 1 year

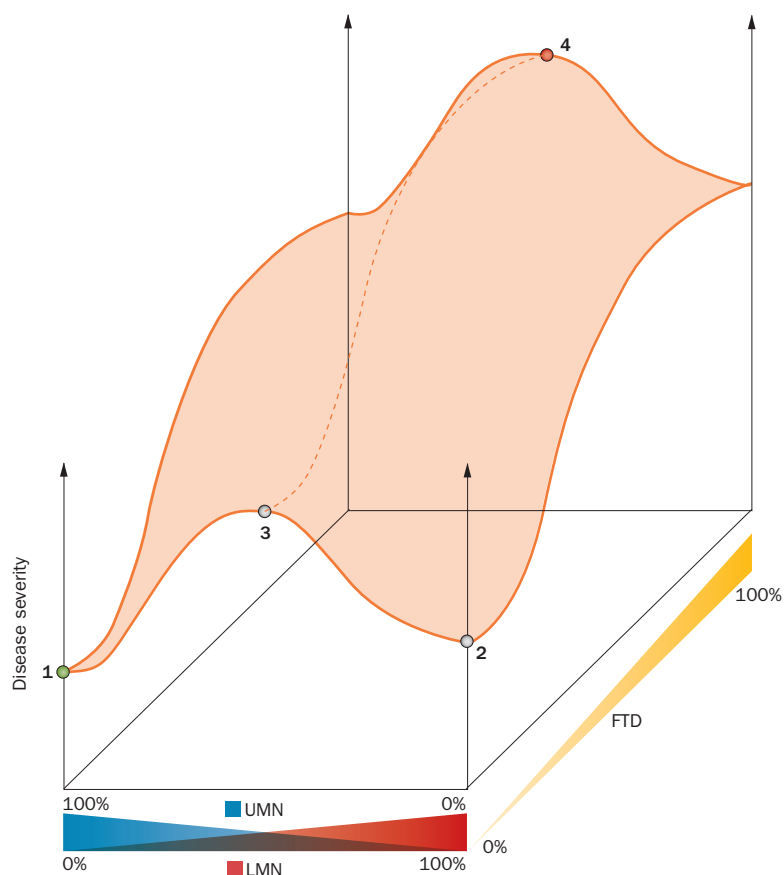


Figure 5 | Disease severity correlates with extent of neuronal involvement. In ALS, UMN, LMN and frontotemporal neurons are affected to variable extents, resulting in a wide range of clinical representations and disease severity, which is reflected by large prognostic variability. The horizontal axis depicts the proportion of UMN versus LMN involvement, and frontotemporal involvement is depicted in the diagonal axis. Disease severity is depicted in the vertical axis, and correlates inversely with survival. In the UMN–LMN spectrum, pure UMN involvement, as in PLS (1), and pure LMN involvement, as in PMA (2) have a better prognosis than disease with both UMN and LMN involvement (3). Increasing frontotemporal involvement is associated with shortened survival. Degeneration of all three neuronal systems (4) is associated with the highest disease severity and, hence, the worst prognosis. Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; LMN, lower motor neuron; PLS, primary lateral sclerosis; PMA, primary muscular atrophy; UMN, upper motor neuron.

less than in pure ALS.⁵⁸ Problems with compliance with therapy and support could contribute to this difference.^{52,59} Alternatively, the difference in prognosis might simply reflect the disease burden (Figure 4).

Lessons from *C9orf72* expansions

The clinical observations discussed above establish a clear link between ALS and FTD. Pathogenic evidence for such link came from the observation that very similar aggregates containing TDP-43, among other proteins, can be found in brain tissue in the majority of patients with either FTD or ALS.⁶⁰ However, it was the discovery of a hexanucleotide expansion mutation in the *C9orf72* gene—*C9orf72*^{(GGGGCC)*exp*}—that unequivocally linked the two ends of the spectrum.^{61–63} This mutation underlies nearly half of cases of familial ALS and a quarter of cases of familial FTD.¹ The pathogenic mechanisms underpinning the connection between *C9orf72*^{(GGGGCC)*exp*}

and ALS–FTD remain poorly understood, but the studies connecting the two have already changed our perceptions of these neurodegenerative disorders.²

Patients with *C9orf72*^{(GGGGCC)*exp*}-associated ALS show marked phenotypic variability. In patients from within the same family with a *C9orf72* expansion, onset can be frontotemporal, bulbar or spinal.^{64,65} The length of the repeat section does not seem to correlate with the severity of disease or site of onset, and patients who are homozygous for the mutation do not have more-severe disease than heterozygous patients.⁶⁴ Bulbar onset is more frequent in ALS patients with *C9orf72*^{(GGGGCC)*exp*} than in those without.⁶⁴ Interestingly, bulbar onset is (almost) never seen in mutant-*SOD1*-associated ALS, and cognitive impairment is equally rare in patients with this mutation.^{12,66,67} It should be noted that cognitive assessment in patients with bulbar failure can be challenging because of the speech problems and pseudobulbar affect that these patients experience, and instruments for bedside evaluation are still being developed.

The spectrum of neuropsychiatric symptoms associated with *C9orf72*^{(GGGGCC)*exp*}-associated ALS is much broader than previously thought, even encompassing psychosis and depressive pseudodementia.^{53,64,65,68,69} Furthermore, motor symptoms in these patients can be variable, manifesting as ataxia, parkinsonism or chorea (discussed below).

In conclusion, FTD and ALS form a spectrum, with ‘pure ALS’ and ‘pure FTD’ at the extreme ends. The factors that modify the phenotypic expression and, thus, determine a patient’s position on that continuum are unknown. The biological basis of such a disease continuum is likely to be complex, which is already evident from the observation that the ‘FTD’ component seems to be susceptible to different modifying factors than the ‘ALS’ component, as discussed below.

ALS as a multisystem degeneration

Although the symptoms and signs in a patient with ALS are predominantly motor in nature, it should be kept in mind that the lines defining neurodegenerative disorders are blurring. Some evidence for this phenomenon again comes from the study of *C9orf72*^{(GGGGCC)*exp*}. This mutation gives rise to clinical characteristics well beyond ALS–FTD: it can also manifest as cerebellar abnormalities and autonomic dysfunction, leading to a diagnosis of multiple system atrophy, or as chorea and neuropsychiatric abnormalities, leading to a diagnosis of Huntington disease (HD).^{70,71}

Surprisingly, some genes associated with ALS–FTD can also influence phenotypic traits that are not directly related to the function of the nervous system. Mutations in *VCP*, *HNRNPA2B1* and *HNRNPA1* can induce ALS and/or FTLD combined with inclusion body myositis and bone abnormalities, such as those seen in Paget disease.^{72,73} These phenotypes again demonstrate the multisystemic character of ALS.

Evidence for the widespread nature of ALS-induced pathology has also come from the careful clinical observation of patients with unusually long survival in the

setting of sustained ventilatory and nutritional support. In these patients, eye movement abnormalities, autonomic dysfunction and sensory involvement eventually become evident.⁷⁴ In rare cases, such multisystem involvement is already apparent at disease onset, and sometimes the clinical presentation is so different from that of classic ALS that clinicians consider the patient to have a different disease. In the sections that follow, we discuss some of these presentations.

ALS with extrapyramidal involvement

Besides the endemic ALS–Parkinson dementia syndromes of Guam⁷⁵ and the Kii peninsula,⁷⁶ extrapyramidal involvement can sometimes be observed in patients with ALS. ALS associated with Parkinson disease (PD) is known as Brait–Fahn–Schwartz syndrome or ALS–PD complex, and is very rare.⁷⁷ The parkinsonism in these patients is usually typical for PD, including the response to levodopa.⁷⁸ Onset of motor neuron dysfunction usually follows a few years later, but simultaneous onset has been reported.^{77,79} Progression is similar to that of classic ALS.⁷⁸ These rare patients are thought to have two separate diseases, although mutations in *PARK7* (also known as *DJ1*) have been reported to cause a PD–ALS–FTD syndrome, providing a possible genetic link.⁸⁰

ALS–parkinsonism is much more common than ALS–PD complex. ALS–parkinsonism refers to the presence of extrapyramidal findings that are unresponsive to levodopa in patients with ALS. Mild parkinsonism is present in 5–15% of patients with ALS, and is typically characterized by postural instability and backward falls.^{78,81} In such patients, abnormalities in the nigrostriatal system can be seen on dopamine transporter imaging or at autopsy.^{78,81–83} In our experience, distinguishing the spastic, extrapyramidal and frontal motor findings in such patients is not trivial, which could explain why different studies have reported variable frequencies of ALS–parkinsonism.

Chorea and/or hemiballismus can occur late in the disease course in rare cases of ALS.^{84,85} As mentioned above, chorea is seen in some patients with a *C9orf72* mutation. To date, about 15 cases of ALS–chorea—concomitant ALS and HD—have been reported.⁸⁶ Most of these patients have late-onset (>50 years) HD, and developed ALS 5–10 years later.⁸⁶ Neuropathological evidence for motor neuron involvement has been reported in a subset of patients with HD.⁸⁷

ALS and cerebellar ataxia

Ataxia is a rare finding in ALS. As mentioned above, it is known to occur in patients with *C9orf72*^{(GGGGCC)^{exp}}. In addition, a few patients with spinocerebellar ataxia (SCA) have been reported to develop rapidly progressive ALS in the late stage of their disease (SCA–ALS).^{70,88} Interestingly, SCA type 2, which is caused by a CAG expansion in *ATXN2*, has genotypic and phenotypic overlap with ALS. Intermediate-length expansions in *ATXN2* are a risk factor for ALS—but, strangely enough—not for ALS–FTD or FTD^{89,90}—and *ATXN2* mutations can present as ALS.⁹¹ The biological basis for the link between SCA and ALS is unknown.

ALS with sensory involvement

Subjective sensory symptoms are reported to occur in 50%, and objective sensory signs in 10%, of patients with ALS, but a true sensory neuropathy is rare in ALS.⁹² The *SOD1*^{D90A} mutation gives rise to prominent sensory symptoms, with posterior column involvement evident at autopsy.^{14,93,94}

ALS with urinary and autonomic involvement

Apart from patients with a *C9orf72*^{(GGGGCC)^{exp}} mutation,⁹⁵ symptoms indicative of autonomic nervous system involvement are rare in ALS, although specific testing can indicate subclinical involvement of cardiovascular, gastrointestinal and sudomotor systems, and the salivary and lacrimal gland.^{96,97} Bladder problems are commonly believed not to be a feature of ALS, because Onuf's nucleus is typically spared or only minimally affected.³ Of note, urinary incontinence and retention certainly do occur in patients with ALS, but these problems are usually attributed to the use of muscle relaxants and anticholinergics, or to the patient's motor problems. However, it should be noted that patients with *SOD1* Asp90Ala mutations often have urinary symptoms,^{14,94} and that urgency of micturition is a very frequent symptom of PLS, affecting 50–70% of patients.^{45,98}

ALS with ophthalmoplegia

As mentioned above, ophthalmoplegia, resulting from widespread brainstem pathology, can be observed in very late stages of ALS, and is only seen in patients with unusually long survival; it very rarely occurs shortly after disease onset.

ALS with deafness

Deafness is not a feature of ALS or any of its genetic or phenotypic variants; however, it can be part of rare syndromes with ALS-like features, the most famous of which is Brown–Vialletto–Van Laere syndrome, a genetic disease caused by mutations in genes coding for riboflavin transporters.⁹⁹ This syndrome is closely related to Fazio–Londe syndrome, in which auditory function is spared.³

Summary

In summary, the extrapyramidal, cerebellar, sensory or autonomic systems are rarely affected by ALS, and usually only with advanced disease. Similarly, urinary and ocular motor neuron involvement is only seen in patients with very long survival and advanced disease. Disruption of these systems usually has limited clinical importance, but it confirms the viewpoint that ALS is a multisystem neurological disease.

From biology to therapy

As described above, ALS has high phenotypic variability. Some of the phenotypic differences might be of a quantitative rather than a qualitative nature, as their detection depends on the method of observation. For example, if sophisticated testing is used, all patients with ALS might show evidence of frontal dysfunction,¹⁰⁰ and transcranial

magnetic stimulation of the cortex might uncover corticospinal abnormalities that would go unnoticed by a clinical examination.¹⁰¹

The molecular and cellular biology underlying the phenotypic variation remain elusive. Motor neurons seem strikingly vulnerable to ALS, those with a large diameter more so than small ones,^{102,103} whereas the oculomotor neurons and those in Onuf's nucleus are far more resistant. Why ALS starts in spinal neurons in some patients, but in bulbar neurons in others, remains puzzling. The large layer V neurons in the frontal and temporal cortex are generally less vulnerable than motor neurons, but in some patients this situation is reversed. Why do some patients with *C9orf72*^{(GGGGCC)^{exp}} develop ALS, whereas others develop FTD or ALS-FTD? Why do some patients with the *SOD1* Gly93Cys mutations die after 2 years of disease, while others with the same mutation survive for more than 20 years? Why do some individuals carrying a pathogenic *SOD1* or *C9orf72* mutation never get ALS or FTD? Are they resistant to the disease, or is their age at onset beyond the normal human lifespan?

Several factors contributing to different aspects of this vulnerability have been identified, but the pathophysiological mechanisms remain poorly understood. The size of the motor neurons, the length of their axons, their metabolic rate and many other characteristics have been hypothesized as contributors, but never proven to have a role. Some evidence suggests that the low abundance of calcium buffering proteins¹⁰⁴ and the presence of mitochondrial matrix metalloproteinase-9¹⁰⁵ underlie the difference in vulnerability between oculomotor and other motor neurons. Expression of the ephrin type-A receptor 4 protein (encoded by *EPHA4*),¹⁰⁶ as well as excitability characteristics,¹⁰⁷ have been suggested to contribute to the difference in vulnerability of large versus small motor neurons. Susceptibility of motor neurons to excitotoxicity could explain why spinal sensory neurons are less vulnerable to ALS than are motor neurons.¹⁰⁸ Moreover, studies in *SOD1* mutant mice suggest that the vulnerability of motor neurons is related to specific excitability-related pathways in these cells.¹⁰⁷

Polymorphisms in the *UNC13A* gene and expression levels of *EPHA4* have been suggested to contribute to the variability in disease severity.^{106,109} *ATXN2* expansions are a risk factor for ALS but not for FTD,⁹⁰ whereas the *TMEM106B* risk allele is a risk factor for FTD but not for ALS.¹¹⁰ Phenotypic variability across the ALS-FTD spectrum (and probably other spectra) is, thus, believed to be largely due to various genetic polymorphisms with different cytotoxic or cytoprotective effects according to neuronal cell type. Better knowledge of these factors,

whether they be environmental or genetic in nature, is important, as they could be targets for intervention, even in patients in whom the cause of the disease is unknown.

Conclusions

Since its initial description by Charcot, ALS has been considered to be a homogenous neurodegenerative disease with selective involvement of both upper and lower motor neurons. Progress in genetics and in precise phenotyping of ALS has revealed shortcomings in the 19th century semiological approach. Abundant evidence has redirected the view towards the concept of a heterogeneous multi-system neurodegenerative disease. Cognitive impairment is thought to be an intrinsic characteristic of this disease, as reflected in the ALS-FTD spectrum. Involvement of upper and lower motor neurons forms a similar spectrum. Variability in clinical presentation, onset, duration and heritability is considerable. Clinically relevant involvement of extrapyramidal, cerebellar, autonomic and sensory systems is rare, but shows ALS to be a multisystem degeneration disorder.

Some of the clinical variability certainly depends on the method and timing of assessment, but the majority seems to reflect differences in vulnerability of neurons. Clinical, genetic and biological studies are underway to identify the factors that underlie this variability. It is unknown whether this variability also implies differential response to therapy. It remains to be seen whether all phenotypic presentations will respond to the same drug and, if so, to the same extent. Phenomics, genomics, proteomics, metabolomics and other unbiased approaches will need to be brought together. Such approaches will require large sets of very carefully and uniformly phenotyped patient populations. Hopefully, such studies will allow the development of strategies to change the phenotypic expression of ALS and find a cure for this dreadful disease.

Review criteria

PubMed was searched for articles published in English from January 1990 to August 2014. The following search terms were used either individually or in combination: "ALS", "onset", "presentation", "survival", "age", "bulbar", "flail arm", "flail leg", "Mills", "PLS", "PMA", "UMN", "LMN", "FTD", "cognitive", "extrapyramidal", "Parkinson", "chorea", "ataxia", "ophthalmoplegia", "urinary" and "genetics". Reference lists of selected papers were also searched for further leads. For most papers, full-text articles were obtained. Papers were selected for their relevance, with a preference for recent articles. Additional relevant papers known to the authors were also included.

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Author contributions

B.S. and W.R. researched data for the article. Both authors made substantial contributions to discussions of the content, writing the article, and reviewing and/or editing of the manuscript before submission.

BAILES

EXHIBIT 14

REVIEW

The Prevalence of Parkinson's Disease: A Systematic Review and Meta-analysis

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ABSTRACT: Parkinson's Disease (PD) is a common neurodegenerative disorder. We sought to synthesize studies on the prevalence of PD to obtain an overall view of how the prevalence of this disease varies by age, by sex, and by geographic location. We searched MEDLINE and EMBASE for epidemiological studies of PD from 1985 to 2010. Data were analyzed by age group, geographic location, and sex. Geographic location was stratified by the following groups: 1) Asia, 2) Africa, 3) South America, and 4) Europe/North America/Australia. Meta-regression was used to determine whether a significant difference was present between groups. Forty-seven studies were included in the analysis. Meta-analysis of the worldwide data showed a rising prevalence of PD with age (all per 100,000): 41 in 40 to 49 years; 107 in 50 to 59 years; 173 in 55 to 64 years;

428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80. A significant difference was seen in prevalence by geographic location only for individuals 70 to 79 years old, with a prevalence of 1,601 in individuals from North America, Europe, and Australia, compared with 646 in individuals from Asia ($P < 0.05$). A significant difference in prevalence by sex was found only for individuals 50 to 59 years old, with a prevalence of 41 in females and 134 in males ($P < 0.05$). PD prevalence increases steadily with age. Some differences in prevalence by geographic location and sex can be detected. © 2014 International Parkinson and Movement Disorder Society

Key Words: prevalence studies; risk factors in epidemiology; Parkinson's disease/Parkinsonism

Parkinson's disease (PD) is among the most prevalent neurodegenerative conditions. Although its cause remains unknown, many investigators believe that the disease arises from an interaction between genetic and environmental factors that leads to progressive degeneration of neurons in susceptible regions of the brain. Despite decades of investigations, the identity of most

of these factors, the nature of their interaction, and the molecular pathways of neurodegeneration that they initiate remain poorly understood.

Epidemiological data regarding the prevalence of PD are of interest for their potential to identify risk factors and improve understanding of the condition's natural history. Increasingly, these data have also been used to guide effective planning of medical services. Most economically developed and many developing countries are experiencing marked demographic shifts, with progressively larger proportions of their populations entering old age. Because PD affects predominantly older persons, many countries around the world are facing a future of unsustainable demands on limited healthcare resources.

One of the great challenges in studying the epidemiology of PD is that prevalence estimates for the condition have varied widely across studies and countries. Environmental and genetic factors are routinely

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proposed to explain the observed variability, but these likely only capture a portion of the variance. The variable demographics of the populations studied and the marked differences in the methodologies of the studies have likely had a profound effect on outcomes. For example, studies that have relied on medical records to generate an estimate of prevalence exclude from their estimates individuals who have not been seen by physicians for their condition, and individuals who have been seen by physicians but were misdiagnosed as not having the condition.¹ Those studies that have relied on the analysis of drug consumption data in a given region can be confounded by numerous other factors, including culturally determined treatment practices, and variable access to reimbursement for medications that vary by country and region.²

In theory, case ascertainment through door-to-door or population-based random sampling offers a more robust alternative. The latter approaches have the advantage of including those patients who have not sought medical attention and those who have not had adequate access to medical care, and should in theory be more suitable for international comparisons. These approaches, however, are expensive, and in some instances may be impractical because of legislative restrictions on the use of personal data.³

This systematic review examines the prevalence of PD worldwide with a meta-analysis of published, door-to-door or population-based random sampling assessments of the condition. The study took place as part of a larger effort initiated by the Public Health Agency of Canada to determine the incidence and prevalence of 15 neurological diseases.

Methods

Selection of Studies

Search strategies for studies on the prevalence of PD were developed in consultation with an academic research librarian with expertise in systematic review. Studies on the incidence of PD are discussed in a separate manuscript.

Both MEDLINE and EMBASE databases were searched using terms specific to PD, and restricted to studies of prevalence and epidemiology (see Supplemental Data Appendix e-1). The sensitivity of the electronic search was checked by comparing relevant references found in the bibliographies of the identified articles against those contained in the database. All studies published in English or French were included. Two independent reviewers screened abstracts to determine whether a full text review should be performed. All studies of door-to-door surveys or random population samples with a physical examination by a health professional to confirm or exclude a diagnosis of PD were included.

We established a date limit of 1985 for study inclusion, because before this date magnetic resonance imaging, which has revolutionized the diagnosis of many neurological disorders, was not in routine clinical use. Our study was part of a larger effort to determine the prevalence of 15 neurological disorders in which magnetic resonance imaging plays a greater diagnostic role than in PD, and our choice of date limit also ensured consistency with the broader research initiative within which we were operating. Review articles or papers using nonoriginal data were also excluded, but their bibliographies were reviewed to ensure additional articles were not missed. In cases in which studies reported duplicate data, the study reporting the most up-to-date and complete data set was included.

Data Extraction

Data extraction was performed in duplicate using a standardized assessment form that included the following domains: Study reference, screening procedure, diagnostic criteria, exclusion criteria, number of PD cases used to estimate prevalence, results, study design, screening personnel, target population. Crude prevalence was reported as cases per 100,000 persons for each study. Breakdown of prevalence by socio-demographic categories (e.g., age, sex) was recorded if given. All data were independently assessed by two reviewers, and the extracted data were entered into evidence tables. If the results of the data extraction differed between the two reviewers, a third reviewer re-assessed the relevant study. Any differences among results were then discussed among the reviewers until consensus could be achieved.

Quality Assessment

A quality assessment was performed for each study based on criteria developed from guidelines on the evaluation of prevalence studies.^{4,5} Studies were given a score of 0 to 8 based on the degree to which they fulfilled 8 criteria relating to the rigor of the clinical assessment, the quality of the statistical analysis, and the extent to which the sample population represented the population at large (see Supplemental Data Appendix e-2 for quality criteria).

Data Synthesis

The Cochrane Q statistic was calculated and I^2 used to quantify the amount of between-study heterogeneity. When significant heterogeneity was absent, the pooled prevalence per 100,000 people and 95% confidence intervals were calculated using a fixed-effects model. When significant heterogeneity was present, a random-effects model was used. With a fixed-effect model, the studies are weighted using the inverse of the variance (larger studies receive more weight), and

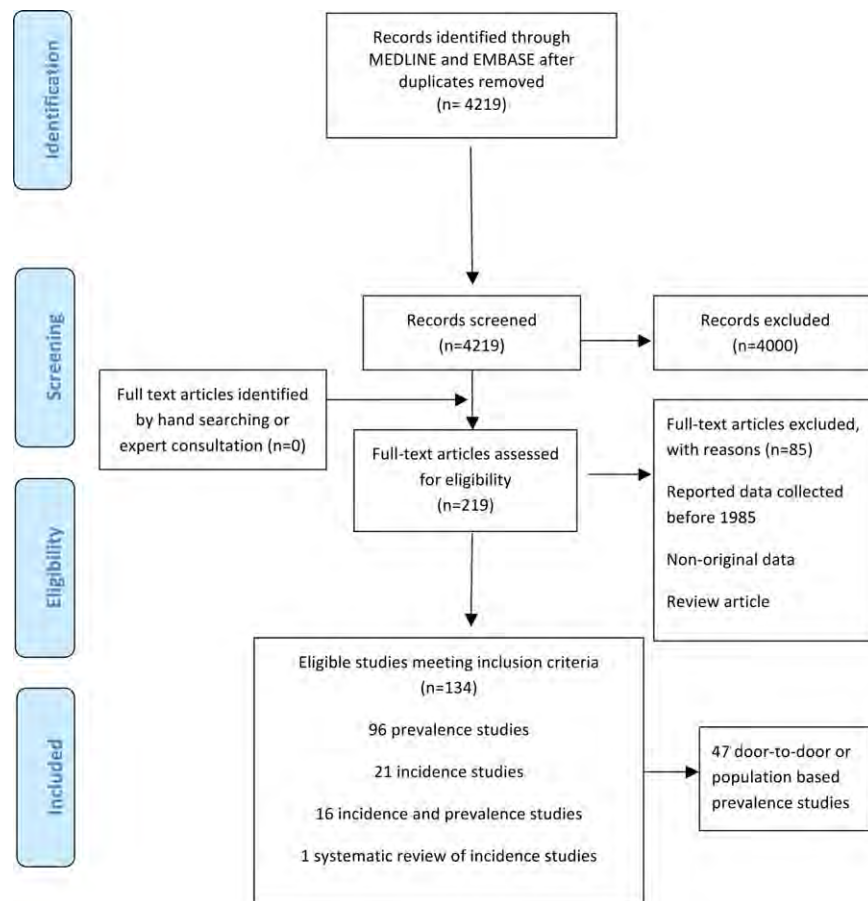


FIG. 1. Flow diagram. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with a random-effects model the inverse variance is corrected by a measure of between-study variation (tau-squared), thus reducing the effects of sample size. Because prevalence is a proportion, study estimates were combined using a log transformation to help normalize the data. Data were analyzed by age group, geographic location, and sex. Geographic location was stratified by the following groups: 1) Asia, 2) Africa, 3) South America, and 4) Europe/North America/Australia. Studies from Europe, North America, and Australia were combined into a single geographic group because of the overall small number of studies performed in each of these locations, and the predominantly white population in each region. Meta-regression was used to determine whether a significant difference was present between groups. A sensitivity analysis of the data was performed by study quality; studies receiving a quality score of 7 or higher were combined using meta-analysis and compared with studies with a quality score lower than 7 to determine whether significant differences were present based on quality.

For all tests, $P < 0.05$ was deemed significant. All statistical analyses were carried out in R version 2.14.⁶ The meta package was used to produce the pooled estimates and forest plots.⁷ The metafor pack-

age was used to conduct the meta-regression, using restricted maximum likelihood estimation.⁸

Results

The combined MEDLINE and EMBASE searches (conducted in December 2010) yielded 4,219 abstracts (see Fig. 1, Prisma Flow Diagram). Two hundred nineteen full-text articles were reviewed. We identified 112 studies on the prevalence of PD, with 47 of these studies using a door-to-door survey or random population sample that included a physical examination by a health professional to confirm or exclude a diagnosis of PD.

Of the 47 included studies, 21 were performed in Asia,⁹⁻²⁹ 11 in Europe,^{1,30-39} 5 in Africa,⁴⁰⁻⁴⁴ 4 in Australia,⁴⁵⁻⁴⁸ 4 in South America,⁴⁹⁻⁵² and 2 in North America^{53,54} (see Supplemental Data Table e-1). Most studies used a two-stage procedure to identify individuals with PD. In stage 1, screening questionnaires were administered (usually in person, and rarely by mailed questionnaire) to elicit symptoms of PD. In stage 2, individuals who screened positive in stage 1 were examined by a health care professional (usually a neurologist) to confirm or refute a diagnosis

TABLE 1. PD prevalence by study quality (per 100,000)

Age Group	All Included Studies	Studies with Quality Score 7+	Studies with Quality Score <7
40-49	41 95%CI 20, 81 I^2 0	Analysis not possible	Analysis not possible
50-59	107 95% CI 54, 211 I^2 85.4	156 95% CI 71, 342 I^2 53	82 95% CI 37, 180 I^2 41.3
55-64	173 95% CI 88, 340 I^2 74	220 95% CI 156, 311 I^2 0	99 95% CI 13, 785 I^2 89.4
60-69	428 95% CI 235, 780 I^2 95	503 95% CI 342, 741 I^2 40.8	383 95% CI 180, 814 I^2 95
65-74	425 95% CI 193, 939 I^2 89	572 95% CI 227, 1439 I^2 52.3	317 95%CI 34, 2951 I^2 96.5
70-79	1,087 95% CI 627, 1,883 I^2 97.4	1,277 95% CI 819, 1,993 I^2 82	980 95% CI 444, 2,161 I^2 98.3
80+	1,903 95% CI 1,132, 3,198 I^2 95.9	2,498 95% CI 1,571, 3,972 I^2 80.7	1,607 95% CI 701, 3,682 I^2 97.6
Overall	315 95% CI 113, 873 I^2 94.5	571 95% CI 243, 1,339 I^2 91.4	251 95% CI 75, 842 I^2 91.2

of PD, and to rule out secondary causes (e.g., drug-induced parkinsonism or vascular parkinsonism) or cases of atypical parkinsonism. Between studies, diagnostic criteria for PD varied, with 2 or 3 cardinal motor signs of PD (rest tremor, bradykinesia, rigidity, impaired postural reflexes, and a 5th sign referred to in some studies) applied in 24 studies; UK brain bank criteria applied in eight studies; EUROPARKINSON diagnostic criteria applied in two studies; National Institute of Neurologic Disorders and Stroke criteria and Schoenberg criteria in one study each. Diagnostic criteria remained undefined in 10 studies. The median quality score was 6, and the mean quality score was 5.9.

Age

Meta-analysis of the worldwide data revealed a rising prevalence of PD with age: 41 per 100,000 in individuals 40 to 49 years; 107 per 100,000 in individuals 50 to 59 years; 173 per 100,000 in individuals 55 to 64 years; 428 per 100,000 in individuals 60 to 69 years; 425 per 100,000 in individuals 65 to 74 years; 1,087 per 100,000 in individuals 70 to 79 years; and 1,903 per 100,000 in individuals over age 80 (Table 1).

We performed a sensitivity analysis on the age-stratified data to determine whether our meta-analysis results differed based on the study quality score (see Table 1). We performed a meta-analysis of high-quality studies (quality score 7 or 8 out of 8 points), and compared this with a meta-analysis of studies with quality scores of 6 or less. Although no statistically significant difference was found by meta-regression in

the age-stratified prevalence estimates grouped by quality score, prevalence estimates in all age groups were higher in the high-quality studies. With the exception of the 50 to 59 age group category, prevalence estimates from high-quality studies also had narrower 95% confidence intervals, and smaller I^2 values, indicating less between-study heterogeneity.

In our analysis of the prevalence of PD by age and geographic location, individuals 70 to 79 years of age in Asia had a significantly lower prevalence of PD (646 per 100,000) compared with individuals of the same age in Europe, North America, and Australia (1,602 per 100,000; $P < 0.05$) (Table 2). The data were insufficient to make comparisons between geographic locations for the age groups 50 to 59, 60 to 69, and over 80.

Sex

The effect of sex on the prevalence of PD was also analyzed and stratified by age group and by geographic location. Worldwide, in the 50 to 59 age group, males had a significantly increased prevalence of PD of 134 per 100,000 relative to females, with a prevalence of PD of 41 per 100,000 ($P < 0.05$) (Table 3). A slight, nonsignificant male preponderance of PD was present in most other age groups. Stratified by geographic location, however, no significant difference in prevalence was found between males and females in any region, although prevalence rates were more equal between males and females in Asia than in other

TABLE 2. Prevalence of PD by age and geographic location (per 100,000)

Geographic location	50-59 years	60-69 years	70-79 years	80+ years
Asia	88 95% CI 39, 201 I ² 87.4	376 95% CI 166, 848 I ² 96.7	646 95% CI 320, 1,345 I ² 95.8	1,418 95% CI 612, 3,285 I ² 95.9
Europe/North America/Australia	113 95% CI 49, 261 I ² 0	540 95% CI 373, 781 I ² 0	1,602 95% CI 1,219, 2,105 I ² 67.9	2,953 95% CI 1,936, 4,503 I ² 80.1
South America	228 95% CI 90, 579 I ² 11.3	637 95% CI 377, 1,074 I ² N/A	2,180 95% CI 1,335, 3,559 I ² 55.7	6,095 95% CI 1,975, 18,813 I ² 91

regions (Europe/North America/Australia, Asia, or South America) (Table 4).

Discussion

General Comments on Methodology

Our analysis has identified a number of intriguing differences in prevalence rates of PD related to age, sex, and geographic distribution. Although environmental or genetic factors may be responsible for these findings, as with all meta-analyses, our findings may equally have arisen from confounders within populations or methodological differences within the studies themselves.

For example, small differences in diagnostic and inclusion criteria of the studies included in an analysis can have profound effects on reported prevalence rates. De Rijk and colleagues⁵⁵ have demonstrated in community-based studies that a change in diagnostic criteria for PD may result in a decrease of up to 36% in identified cases.⁵⁵ Differences in methods of ascertainment also may have had a significant impact on the reported rates of PD across studies. The specific content of any questionnaire used for the assessment of PD is a major source of variance. Some questionnaires may have relatively few questions relating specifically to PD,⁴⁶ and where content may indeed relate to parkinsonism, the specific questions may be highly variable. The ability of questionnaires to identify PD signs has been a matter of debate, because recent studies have highlighted their poor sensitivity and specificity for the detection of mild PD signs early in the disease.⁵⁶ Others have found that the sensitivity of screening for neurological disorders may be increased with the addition of physical tasks to symptom questionnaires.⁵⁷ As screening questionnaires to identify putative cases were used in the first stage in most of the studies included in our analysis, disease prevalence may be underestimated because of failures to capture the mildest cases.

TABLE 3. Prevalence of PD by sex and age group (per 100,000)

Age Group	Female	Male
40-49 years	45 95% CI 18, 113 I ² 0	36 95% CI 15, 86 I ² 0
50-59 years	41 95% CI 24, 71 I ² 29.3	134 95% CI 63, 285 I ² 86
55-64 years	150 95% CI 75, 30 I ² 44.8	233 95% CI 120, 452 I ² 53.2
60-69 years	392 95% CI 202, 762 I ² 93.2	389 95% CI 211, 715 I ² 90.7
65-74 years	610 95% CI 322, 1,157 I ² 78.1	706 95% CI 389, 1,280 I ² 78.3
70-79 years	813 95% CI 433, 1,524 I ² 95.8	932 95% CI 494, 1,757 I ² 95.6
80+ years	1,517 95% CI 840, 2,740 I ² 90.3	2,101 95% CI 918, 4,809 I ² 92.3

The level of training of the screening personnel who are performing the initial screen to identify patients with parkinsonism also may be reasonably expected to influence ascertainment. Review of the included studies indicates that the personnel screening subjects for PD had widely differing levels of training and clinical experience, although neurologists or movement disorder subspecialists typically performed physical examinations of cases screening positive. This wide range of expertise becomes especially important when one considers that up to 24% of the diagnoses of PD are incorrect when compared with pathological diagnoses.⁵⁸

Our sensitivity analysis based on study quality failed to show a significant difference in prevalence estimates based on study quality. However, prevalence estimates using higher-quality studies were higher in all age groups, with narrow confidence intervals, and less between-study heterogeneity, suggesting that the higher-quality studies may provide a more precise estimate of disease prevalence.

TABLE 4. Prevalence of PD by sex and geographic location (per 100,000)

Geographic location	Female	Male
Asia	306 95% CI 184, 511 I ² 98.6	371 95% CI 219, 629 I ² 98.8
Europe/North America/Australia	1,267 95% CI 1,005, 1,595 I ² 82.8	1,535 95% CI 1,188, 1,983 I ² 83.9
South America	808 95% CI 356, 1,832 I ² 88.5	1,267 95% CI 583, 2,752 I ² 89.3

Geographic Variability

Analyses of geographic variation of prevalence are easily confounded by demographic variation between populations. Our meta-analysis attempted to control for the effects of demographic differences with age-specific analyses. Comparing within age groups across regions, our study identified in the 70- to 79-year-old population a significantly lower prevalence of PD in Asia than in North America, Europe, and Australia, as well as a lower prevalence of PD (not reaching statistical significance), in all other age groups in Asia compared with other regions. Caveats relating to methodological differences aside, genetic or environmental susceptibilities to PD could reasonably explain these findings.

Age

Our meta-analysis identified a steady increase in PD prevalence with age across all regions of the world. This finding is in agreement with some studies,^{33,59} and is in contradistinction to others that have reported a peak at approximately age 70 followed by decreasing prevalence by the age of 80 and thereafter.^{34,60} One interpretation for the previously reported decline in prevalence among the oldest old is that it is caused by under-ascertainment of PD among older subjects, which occurs when patients are detected through medical records only.¹ Regardless of the possible explanations, the interpretation of all age-related data must be undertaken with the understanding that the numbers of patients of advanced age in any given study are generally small, and a few reported cases can therefore have a significant impact on results. A systematic review of incidence studies of PD found that most studies have reported that PD incidence rises steadily with age to a peak occurring between the ages of 70 to 79. A few studies have reported that PD incidence continues to increase in those aged 80 and older.⁶¹

Sex

Finally, our study demonstrated sex differences in worldwide PD prevalence rates between males and females, with a lower prevalence of PD noted in females than in males in the 50- to 59-year age group. From a neurobiological perspective, some support for this finding may be seen in Haaxma et al.'s study⁶² reporting that women, once they acquire PD, may have a more benign phenotype with slower progression of disease than men. The authors have speculated that this phenotypic difference is attributable to higher estrogen activity, which leads in turn to higher dopamine levels in the striatum.⁶² A systematic review of incidence studies of PD reported a significantly greater incidence of PD in men than in women in most of the studies that have provided age-standardized sex ratios,

and that onset of disease in men was often slightly earlier than in women.⁶¹

Changes over time in the incidence of PD and the length of survival of individuals with PD will affect PD prevalence. Although we did not perform a time trend analysis of PD prevalence, one might expect the prevalence of PD to increase over time because of increases in incidence or improved survival. Data from England and Wales have shown decreasing PD mortality rates in both men and women from 1993 to 2006, potentially because of improvements in PD treatments and general medical care.⁶³

The results of our systematic review have brought to light intriguing differences in the prevalence of PD reported by geographic region, age, and sex; however, it has also served to emphasize the problems inherent in performing epidemiologic evaluations across widely disparate populations, cultures, and regions. Very few of the available studies included in our analysis could be said to be without methodological flaws; and the variability of methodological approaches applied across studies precludes simplistic comparisons. A consensus statement on the minimal scientific standard for prevalence studies would improve the quality and consistency of subsequent studies attempting to move beyond our own.

The results of our own study suggest the possibility of racial and geographic variation in the prevalence of PD. These findings argue for further epidemiologic surveys, specifically with high-quality screening instruments for PD and confirmation of diagnoses with sensitive, internationally accepted diagnostic criteria to ensure greater comparability.⁶⁴ Additional, longer-term prospective studies would help establish whether the clinical progression and prognosis of the disease differs between racial groups and among different parts of the world.

Where reliable differences in prevalence can be demonstrated between populations, opportunities may arise for more refined molecular epidemiology of PD, allowing more direct attempts to identify alleles that differ in type and frequency across populations to influence disease susceptibility, progression, or treatment response.

The potential for these important scientific insights aside, an equally pressing imperative for the development of accurate prevalence estimates of PD lies in the need to prepare for the effects of the demographic shift that is currently taking place in many regions of the world. An accurate estimate of the magnitude of disease burden will be a necessary first step for efforts to mitigate a projected wave of neurodegenerative disease that threatens to overtake the already beleaguered public health infrastructures of many of the world's mature economies. ■

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Supporting Data

Additional supporting information may be found in the online version of this article at the publisher's web-site.

BAILES

EXHIBIT 15

Juvenile Parkinsonism

Epidemiology, Diagnosis and Treatment

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Abstract

Juvenile parkinsonism, with onset prior to age 21 years, is a relatively rare syndrome. It is caused by a group of heterogeneous entities that can present with a clinical picture similar to idiopathic Parkinson's disease or manifest parkinsonism as part of a spectrum of other signs. Diagnostic testing is guided by the presenting symptoms and aimed at uncovering potentially reversible and/or treatable causes. If an underlying condition is found, treatment is tailored accordingly. Otherwise, treatment is symptomatic and relies on medications commonly employed to treat idiopathic Parkinson's disease. Juvenile parkinsonism patients tend to be plagued by treatment-induced complications, so caution must be employed.

The four cardinal features of Parkinson's disease are tremor at rest, rigidity, bradykinesia/akinesia (slowness or absence of movement) and loss of postural reflexes.^[1] Other signs such as dysphagia, dystonia, autonomic dysfunction, sensory abnormalities and cognitive and neuro-behavioural abnormalities can also appear. The term 'parkinsonism' refers to any combination of parkinsonian features, whether or not they are due to idiopathic Parkinson's disease. Features that suggest a diagnosis other than idiopathic Parkinson's disease include: absence of rest tremor; early dysautonomia; gait dysfunction/postural

instability; hallucinations/dementia; prominent ophthalmoparesis; and atypical features such as ataxia or seizures.^[1]

Early-onset parkinsonism is defined as the onset of a parkinsonian syndrome prior to 40 years of age.^[2] The incidence of parkinsonism increases with age, with an incidence of 0.5 per 100 000 for persons <40 years of age, as compared with 13.4 per 100 000 overall for the general population.^[3] Cases with apparent idiopathic Parkinson's disease onset between age 21 and 40 years are termed young-onset Parkinson's disease.^[4] Approximately 5% of patients referred to specialists for

evaluation of parkinsonian symptoms have onset prior to age 40 years; in Japan the figure is closer to 10%, possibly due to the higher rates of parental consanguinity and recessive early-onset parkinsonism that have been reported.^[4,5] Young-onset Parkinson's disease is clinically and pathologically similar to older-onset Parkinson's disease.^[5,6] The progression of young-onset Parkinson's disease tends to be slower but there is an earlier onset of levodopa treatment complications.^[4] Patients with young-onset Parkinson's disease have more prevalent dystonia but a lower incidence of cognitive deterioration and postural instability.^[4,5]

Onset of parkinsonism prior to age 21 years is termed juvenile parkinsonism.^[7,8] This was first described nearly a century ago, but remains a relatively rare entity.^[7,8] Juvenile parkinsonism patients have demonstrated varied pathological findings at autopsy.^[4] Only one autopsied case of juvenile parkinsonism has had Lewy bodies, the histological marker of Parkinson's disease.^[9] Although some cases of juvenile parkinsonism may represent idiopathic Parkinson's disease, most are likely other conditions.^[7,8]

1. Epidemiology

Quinn et al.^[10] described four patients with onset of symptoms prior to age 21 years in a group of 60 patients with early-onset parkinsonism (7%), and all four had a family history of early-onset parkinsonism. All four patients had akinesia and rigidity, and three patients had tremor. The incidence of parkinsonism in relatives of juvenile parkinsonism patients was higher than that of the general population, while the incidence of parkinsonism in relatives of young-onset Parkinson's disease patients did not differ from the general population.^[10] The median age of onset of symptoms in these juvenile parkinsonism patients was 18 years (range 17–20 years). This study attempted to exclude secondary causes of parkinsonism, such as Wilson's disease. At the 10-year follow-up, one patient had developed dementia at age 33 years and another died at age 62 years.^[5]

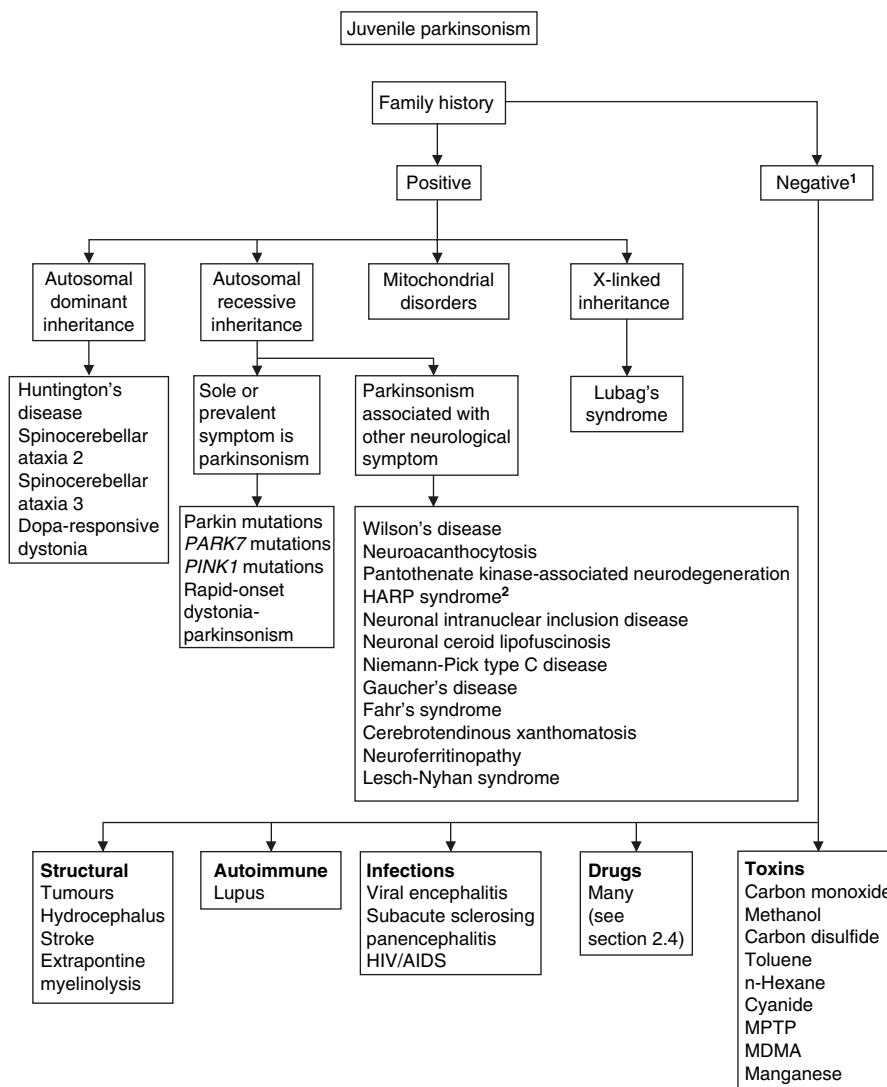
A later study by the same group evaluated 149 patients with early-onset parkinsonism (which included the 60 patients from the earlier study^[10]),

ten of whom had onset prior to age 21 years (7%).^[5] The median age of onset of symptoms in the juvenile parkinsonism patients was 17 years (range 5–19 years) and the male-to-female ratio was 4:1. Fifty percent had a family history of parkinsonism. Nine patients had a good response to levodopa, but all developed dyskinesias and motor fluctuation after a median of 6 months of treatment. At symptom onset, six had dystonia, five had tremor and two had an akinetic-rigid state. Two patients developed painful dystonic spasms and one patient developed dementia. In two patients, ¹⁸F-dopa positron emission tomography (PET) showed reduced striatal uptake. One patient required pallidotomy to ameliorate severe dyskinesias.

Another group reported six patients with juvenile parkinsonism in a cohort of 918 patients of all ages with parkinsonism (0.7%). In this study, only one of the six juvenile parkinsonism patients had a family history of parkinsonism.^[11] The mean age of onset was 12.5 years (range 7–19 years) and the male-to-female ratio was 5:1. All patients responded to levodopa, but four developed early treatment complications and one required stereotactic surgery. All six patients manifested bradykinesia, rigidity and postural instability, five patients had tremor, five had dementia and four had dystonia. This study did not exclude patients with atypical features, such that of the six patients five had supranuclear gaze palsy, three had seizures, one had decreased reflexes, one had multifocal myoclonus and one had pyramidal signs. One patient was diagnosed with Niemann-Pick type C disease. Two patients had cortical atrophy on neuroimaging and one had mid-brain atrophy.

2. Conditions Causing Juvenile Parkinsonism and their Diagnosis

As noted above, Lewy bodies are only rarely seen in juvenile parkinsonism, suggesting that idiopathic Parkinson's disease is not a common cause of this syndrome. The differential diagnosis of juvenile parkinsonism encompasses many entities including genetic causes of parkinsonism, degenerative, metabolic and immune-mediated conditions, infections, structural lesions, toxins and adverse effects of medications (figure 1).^[7,8]



¹ Patients with autosomal recessive conditions may not have affected siblings.

² Hypopre- β -lipoproteinaemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration.

Fig. 1. Differential diagnosis of juvenile parkinsonism. **MDMA** = 3,4-methylenedioxymethamphetamine (ecstasy); **MPTP** = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

2.1 Genetic Causes

Mutations in three genes are known to cause juvenile parkinsonism: parkin (*PARK2*, chromosome 6q), PTEN-induced putative kinase 1 (*PINK1*, previously known as *PARK6*, chromosome 1p) and *PARK7* (also known as *DJ1*,

chromosome 1p). Each of these mutations is associated with autosomal recessive parkinsonism.^[12] Although typically found in early-onset disease, these mutations can also cause late-onset parkinsonism (>40 years).^[12]

Parkin mutations account for the majority of juvenile parkinsonism cases that resemble

idiopathic Parkinson's disease.^[13] These patients manifest slowly progressive, levodopa-responsive parkinsonism, typically with severe, early, levodopa-induced motor fluctuations and dyskinesias.^[13,14] Dystonia, particularly of the lower limbs, is common at onset.^[13] Diurnal fluctuations may be present, with symptoms becoming worse later in the day.^[13] Parkin is an E3-type ubiquitin protein ligase involved in the proteasomal degradation of target proteins, including α -synuclein.^[14] The accumulation of these proteins may result in neuronal death in the substantia nigra and locus ceruleus.^[14] Autopsy in patients with parkin mutations has shown depigmentation of the substantia nigra with neuronal loss and gliosis. Lewy bodies are classically described as being absent, but have been present in a small number of cases.^[15] Functional imaging suggests presynaptic dopaminergic dysfunction.^[15]

PINK1 mutations are the second most common cause of early-onset parkinsonism, accounting for 1–9% of cases.^[12,14] Onset is typically prior to age 50 years.^[12,14] Patients with *PINK1* mutations manifest slowly progressive, levodopa-responsive parkinsonism, typically with dystonia at onset.^[14] They may have sleep benefit and psychiatric disturbances.^[14] *PINK1* encodes a mitochondrial protein, so that mutations may result in mitochondrial dysfunction leading to cell damage causing parkinsonism.^[14]

PARK7 mutations account for only 1–2% of cases of early-onset parkinsonism.^[12] These patients also have slowly progressive, levodopa-responsive parkinsonism.^[13] *PARK7* is likely involved in protection from oxidative stress and chaperoning proteins such as α -synuclein.^[14]

Commercial testing is available for parkin and *PINK1*, and testing for *PARK7* may be available through a research laboratory.^[12] Genetic testing may be helpful in juvenile parkinsonism, particularly with a positive family history, as it may help reduce further work-up and confirm the diagnosis.^[12] However, such testing should be undertaken with caution and only after appropriate genetic counselling. Insurance companies are unlikely to pay for this testing because there is currently no available disease-modifying treatment.

2.2 Hereditary and Degenerative Causes

Another genetic cause of juvenile parkinsonism is dopa-responsive dystonia, an autosomal dominant trait with variable penetrance, which presents with limb dystonia and diurnal fluctuation of symptoms.^[16–19] Presentation can vary from focal dystonia or generalized dystonia, a cerebral palsy-like syndrome with pyramidal signs, to a largely parkinsonian syndrome.^[18–20] A trial of levodopa is indicated for all children presenting with any of these symptoms.^[17,18] Dopa-responsive dystonia patients characteristically have a sustained response to levodopa and do not develop treatment complications. Low-dosage levodopa (300 mg/day) is typically sufficient to impressively ameliorate symptoms, and anticholinergic agents may be beneficial.^[17] Imaging to evaluate pre- and postsynaptic dopaminergic function, such as PET or dopamine transporter single photon emission computed tomography (SPECT), is typically normal, in contrast to idiopathic Parkinson's disease.^[21] In dopa-responsive dystonia, phenylalanine loading results in abnormal elevation of plasma phenylalanine levels and reduced levels of tyrosine and bipterin.^[18] The dopa-responsive dystonia phenotype results from mutations in the gene encoding guanosine 5'-triphosphate (GTP) cyclohydrolase, a cofactor that is necessary for the production of dopamine.^[17,18] An autosomal recessive dopa-responsive dystonia phenotype can result from a mutation in the gene encoding tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. This syndrome is also levodopa responsive.^[17,18] Genetic testing may be possible through research laboratories.

Wilson's disease can cause a myriad of symptoms, including juvenile parkinsonism.^[22] Other symptoms include dystonia, tremor (classically proximal, but all tremor types are possible), dysarthria and neuropsychiatric problems.^[15] Testing for Wilson's disease includes serum copper and ceruloplasmin, 24-hour urine copper, detection of Kayser-Fleischer rings on slit-lamp examination of the cornea, and liver biopsy if necessary.^[22] Penicillamine chelation is typically employed, but in some patients this may cause

initial neurological deterioration.^[22] Zinc, trientine hydrochloride and tetrathiomolybdate are also employed in treatment. Levodopa is typically not helpful. The multiplicity of mutations in the *ATP7B* gene on chromosome 13 makes genetic testing for Wilson's disease not generally useful; however, laboratories may screen for the more common mutations.^[23]

Juvenile-onset Huntington's disease (Westphal variant) can manifest as an akinetic-rigid syndrome of parkinsonism.^[24] Associated symptoms include seizures, developmental delay and a precipitous decline.^[7] The inheritance is autosomal dominant with anticipation, resulting in transmission of a larger CAG (cytosine, adenine, guanine) repeat expansion to successive generations, particularly when inherited paternally.^[25] Treatment with amantadine, levodopa and anticholinergic agents may be helpful for the parkinsonian features, but dopaminergic medications must be employed with caution since they present a significant risk of psychiatric and motor complications.^[24] Genetic testing for the causative trinucleotide repeat expansion is readily available.

Spinocerebellar ataxias can cause juvenile parkinsonism, particularly spinocerebellar ataxias 2 and 3. Spinocerebellar ataxia 3 (Machado-Joseph disease) commonly causes parkinsonism that may be juvenile in onset and levodopa responsive.^[26,27] These are both dominantly inherited conditions caused by trinucleotide repeat expansions. The appearance of ataxia, abnormal saccadic eye movements and peripheral neuropathy help to distinguish spinocerebellar ataxia 3 from idiopathic Parkinson's disease.^[28,29] Spinocerebellar ataxia 2 may also cause juvenile parkinsonism; however, prominent ataxia is typically present, in concert with hyporeflexia, dysphagia, pyramidal signs and slowed eye movements.^[26,28,29] Response to levodopa treatment may be variable. Genetic testing is widely available.

Rapid-onset dystonia-parkinsonism presents as an acute onset of dystonia and bradykinesia, which is not levodopa responsive and tends to be stable over long periods of time.^[17] Genetic testing for the *ATP1A3* gene may be available from research laboratories, but the diagnosis is typically made on clinical grounds alone.^[30]

Neuroacanthocytosis may manifest with juvenile parkinsonism; however, chorea, orofacial dyskinesias, dystonia and developmental delay are more typical.^[17,31] The chorea-acanthocytosis gene is located on chromosome 9q21.^[17] Acanthocytes can be detected in peripheral blood smears. Pantothenate kinase-associated neurodegeneration can cause parkinsonism in juvenile patients. This condition presents with symptoms of extrapyramidal, pyramidal and cognitive dysfunction.^[17] The *PANK2* gene encodes pantothenate kinase. Brain MRI imaging shows the 'eye of the tiger' sign due to signal change in the globus pallidus.^[17] HARP syndrome (hypopre- β -lipoproteinaemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration) has similar clinical and imaging findings to pantothenate kinase-associated neurodegeneration.^[2,15] Genetic testing for these conditions may be available through research laboratories. Treatments such as amantadine and anticholinergic agents may be mildly helpful for the parkinsonian features in these conditions, but levodopa is typically ineffective.

Mitochondrial disorders may result in parkinsonism with juvenile onset.^[2,32] Other symptoms typically associated with these disorders include seizures, stroke-like episodes, pyramidal signs and myoclonus.^[15,17] Brain MRI may show hyperintensity in the basal ganglia. Elevated serum lactate is characteristic.^[2] Levodopa is not beneficial.

Neuronal intranuclear inclusion disease is a rare condition that may present with juvenile, levodopa-responsive parkinsonism.^[33,34] In this condition, other neurological signs are typically present including dementia, pyramidal signs and neuropathy.^[33,34] Diagnosis is through rectal biopsy, which demonstrates typical eosinophilic intranuclear inclusions in neurons.^[35] Juvenile neuronal ceroid lipofuscinosis is a lysosomal storage disease that may also present with a juvenile-onset, levodopa-responsive parkinsonian syndrome.^[36,37] Other features often seen in this condition include seizures and vision loss.^[36,37] Diagnosis is by the electron microscopic demonstration of typical fingerprint inclusions in rectal, muscle, skin, conjunctival or brain biopsy.^[2]

Niemann-Pick type C disease may present in juvenile patients with an akinetic-rigid syndrome.^[38] Additional features are typically present, including dementia, ataxia, dystonia, supranuclear gaze palsy and hepatosplenomegaly.^[39] Mutations in the *NPC1* and *NCP2* genes have been found.^[39] Diagnosis is aided by finding sea-blue histiocytes on bone marrow biopsy, as well as reduced cholesterol esterification and reduced sphingomyelinase activity in cultured skin fibroblasts.^[2,39] This condition does not respond to levodopa, but anticholinergic agents may be helpful.

Gaucher's disease is another lysosomal storage disease that can cause a juvenile parkinsonian syndrome.^[40,41] The diagnosis is established by the demonstration of reduced β -glucosidase activity.^[41] Juvenile parkinsonism due to Fahr's syndrome is suggested by a brain CT showing calcification of the basal ganglia.^[17] Cerebrotendinous xanthomatosis may cause an early-onset parkinsonian syndrome, with associated vision loss, neuropathy and hallmark tendon xanthomas.^[42-46] The diagnosis is aided by demonstration of elevated plasma cholestanol.^[42-46] The standard treatment is chenodeoxycholic acid, but improvement of parkinsonism after treatment with an antihistamine drug, diphenylpyraline, has been reported in a small number of cases.^[45] Neuroferritinopathy,^[47,48] Lubag's syndrome (Filipino X-linked dystonia-parkinsonism)^[49] and Lesch-Nyhan syndrome^[50,51] are other rare causes of juvenile parkinsonism. Genetic testing for these disorders, with the exception of neuroferritinopathy, is commercially available. Treatment with antiparkinsonian medications may be helpful in all of these disorders, especially Lesch-Nyhan syndrome.^[52]

2.3 Infectious and Immune-Mediated Causes

Systemic lupus erythematosus may cause a parkinsonian syndrome characterized by an akinetic-rigid state and tremor.^[53] Other manifestations of systemic lupus erythematosus include seizures, neuropsychiatric disturbances and cranial nerve palsies.^[15] Diagnosis is undertaken by evaluation of inflammatory markers such as erythrocyte sedimentation rate, anti-nuclear

antibodies, anti-double-stranded DNA and by CSF analysis.^[2,15] Systemic treatment of systemic lupus erythematosus is indicated and anti-parkinsonian medications may be helpful.

Infections may lead to juvenile parkinsonism. Classically, encephalitis lethargica (von Economo's encephalitis), which some investigators believe followed the influenza pandemic of 1914–18, caused lethargy and cranial neuropathies, but it could also cause an acute akinetic-rigid state and had the potential to lead to postencephalitic parkinsonism years later.^[54,55] Defining features include oculogyric crises, sleep disturbance and akinetic mutism.^[54] This syndrome, seldom if ever seen in recent decades, is often levodopa responsive with frequent treatment complications. Viral encephalitis can cause juvenile parkinsonism, in particular those encephalitides due to Japanese B, Western equine, St. Louis, varicella, mumps and coxsackie viruses.^[56] Diagnostic testing includes viral studies on serum and CSF. Brain MRI may show basal ganglia lesions and EEG may show slowing. Measles virus is responsible for the latent syndrome, subacute sclerosing panencephalitis. It appears years after the initial infection and is levodopa responsive.^[57-59] Associated symptoms include periodic myoclonic jerks, behavioural changes and developmental delay.^[57] Diagnosis is based on clinical evaluation, periodic discharges on EEG and measles antibody titres in serum and CSF. Treatment with interferon- α may be helpful. HIV may lead to parkinsonism, either as a direct consequence of viral-induced cerebral damage or due to an opportunistic infection such as progressive multifocal leukoencephalopathy.^[60,61] Diagnosis is through HIV testing.

2.4 Structural, Toxic and Medication-Related Causes

Structural brain lesions such as tumours including gliomas, meningiomas, ependymomas and craniopharyngiomas may cause symptoms of juvenile parkinsonism by infiltrating the basal ganglia, by compressing the brainstem or, indirectly, by inducing hydrocephalus.^[56,62] Radiotherapy treatment of brain tumours may also

cause parkinsonism.^[63] Other forms of structural pathology with the potential to cause juvenile parkinsonism include: aqueductal stenosis with associated hydrocephalus, stroke affecting the basal ganglia, and extrapontine myelinolysis affecting the basal ganglia. These diagnoses are established by brain imaging. Treatment with antiparkinsonian medications should be considered in these conditions.

Several CNS toxins may lead to juvenile parkinsonism. In carbon monoxide poisoning, the initial presentation is typically cognitive impairment and an encephalitic syndrome, with later, delayed development of parkinsonism.^[64] Other substances, such as methanol, carbon disulfide, toluene, n-hexane, cyanide, manganese, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), may cause juvenile parkinsonism.^[56] These diagnoses are established by history and brain imaging, where basal ganglia abnormalities may be found.^[2] Antiparkinsonian medications may not be effective in these cases or may induce intolerable adverse effects.

Drug-induced parkinsonism may be found in juvenile patients.^[56] Antipsychotic drugs (even those labelled as atypical), dopamine receptor-blocking antiemetics and dopamine-depleting agents (e.g. reserpine and tetrabenazine) are commonly associated with parkinsonism. Other drugs that can cause parkinsonism include certain calcium channel antagonists, captopril, valproate, phenytoin, selective serotonin reuptake inhibitors (SSRIs), lithium, amphotericin B, chloroquine, ciclosporin, vincristine, doxorubicin (adriamycin), vinca alkaloids and cytarabine (cytosine arabinoside).^[56] Drug-induced parkinsonism typically presents with a symmetrical, akinetic-rigid state; resting tremor may also be present. In drug-induced parkinsonism related to the use of dopamine-blocking agents, akathisia and dystonia may also be present, as well as a high-amplitude, low-frequency perioral tremor termed 'rabbit syndrome'. Co-existent tardive dyskinesia in patients taking antipsychotic agents may be a clue to the diagnosis of drug-induced parkinsonism. Functional brain imaging is normal in these patients. Symptoms are reversible on

discontinuation of the offending drug; however, resolution may take up to a year and antiparkinsonian treatment may be necessary in the interim. Anticholinergic medication should be tried initially and amantadine may also be helpful. As a rule, levodopa is not effective and should be used with caution in patients with underlying psychosis.

3. Treatment of Juvenile Parkinsonism

Management of juvenile parkinsonism should first be tailored to the treatment of the underlying conditions in those patients where a secondary cause has been detected.^[56] In cases where correction of the underlying condition is not possible, then symptomatic treatment of parkinsonism may be undertaken. As noted in the discussion of the various diagnoses in section 2, in some circumstances, antiparkinsonian medications may be either contraindicated or not effective. When indicated, medications commonly used to treat idiopathic Parkinson's disease are employed, with dosage adjustment for the paediatric population, as necessary.

Levodopa therapy, in conjunction with a dopa-decarboxylase inhibitor such as carbidopa or benserazide, is the gold standard of treatment for idiopathic Parkinson's disease and may be useful in treating juvenile parkinsonism.^[65-67] Disadvantages in this population include the early development of treatment complications such as motor fluctuations and intolerable dyskinesias.^[2,65-68] Other treatment-limiting adverse effects include orthostasis, psychosis, nausea, sedation (including sudden-onset sleep) and impulse control disorders (pathological gambling, hypersexuality, punding, compulsive shopping and binge eating).^[66,69]

Dopamine receptor agonists may be initially employed as an alternative to levodopa, to delay onset of dyskinesias, but they may not be as efficacious.^[2,7,65-67] As dopaminergic medications, they share the adverse effects listed above for levodopa, but may be more likely to lead to psychosis and impulse control disorders as well as sudden-onset sleep.^[66,68] Accordingly, caution should be employed when using these medications in the juvenile parkinsonism populations as

these patients may be engaged in daily activities requiring alertness and good judgement, such as employment, driving and child care.^[2]

Anticholinergic medications, such as trihexyphenidyl and benztropine, may be beneficial, especially in cases with prominent tremor, dystonia or sialorrhea and those not responding to or not tolerating dopaminergic medications.^[2,7,66] Amantadine is also useful in instances where dopaminergic medications are not indicated and can also help ameliorate dyskinesias.^[2,65,66] Cognitive adverse effects may limit the use of both these medications.^[2,66] An alternative option is a monoamine oxidase B inhibitor (selegiline or rasagiline),^[2,65,66] but these agents do carry a warning about the concomitant use of certain antidepressants and the consumption of tyramine-containing foods, such as red wine, aged cheese and meat. Each of these medications can provide modest symptomatic benefit as monotherapy or as an adjunct to levodopa or a dopamine agonist.^[65,66] Entacapone and tolcapone are catechol-*O*-methyltransferase inhibitors that can be used as an adjunct to levodopa to smooth out motor fluctuations.^[2,7,65,66] However, they can cause problematic dyskinesias and diarrhoea,^[65,66] and tolcapone requires frequent liver function monitoring.^[66]

Botulinum toxin may be useful for prominent dystonia.^[70,71] Atypical antipsychotic agents, especially quetiapine and clozapine, which are the least likely to cause extrapyramidal adverse effects, may be needed to control psychosis, either inherent to the underlying condition or induced by dopaminergic medications.^[69,72,73] Clozapine requires monitoring because of the risk of agranulocytosis, but may be more effective than quetiapine and also has the capacity to reduce levodopa-induced dyskinesias.^[69] Antidepressants and anxiolytic agents may be necessary for the behavioural accompaniments of parkinsonism.^[69] Laxatives may be needed for constipation and peripherally acting anticholinergic agents may be useful for urinary incontinence.^[74] Physical and occupational therapy may be helpful and assistive devices may be needed to aid ambulation.^[74]

Deep brain stimulation is used in the treatment of idiopathic Parkinson's disease;^[75] however, care must be exercised in the consideration of

neuromodulatory surgery in juvenile patients with parkinsonism, as this has not been systematically studied. Deep brain stimulation is employed in treating generalized dystonia in children and as experimental treatment for dystonia in other conditions, such as pantothenate kinase associated-neurodegeneration, Tourette's syndrome^[76-78] and Lesch-Nyhan syndrome.^[79,80] One patient with Lubag's syndrome has benefited from bilateral pallidal deep brain stimulation.^[81] Older patients with known parkin and *PINK1* mutations have benefited from deep brain stimulation surgery, but this finding cannot be readily generalized to those under the age of 21 years at this time (since the youngest patient reported to date was 22 years of age at onset of parkinsonism).^[82-85]

There is much interest in and study of potential new therapeutic options for treating idiopathic Parkinson's disease, such as neurotrophic factors, cell-based therapy, novel neurotransmitter targets and potentially neuroprotective drugs.^[86-89] These agents are of greatest potential benefit for those with a predominantly parkinsonian syndrome due to known mutations in genes such as parkin, *PINK1* and *PARK7*, which involve presynaptic nigral degenerations, but are less likely to be applicable for juvenile parkinsonism symptoms in the context of underlying multisystemic conditions, which include post-synaptic striatal degenerations.

4. Conclusion

Juvenile parkinsonism encompasses a diverse group of entities causing onset of parkinsonian symptoms prior to the age of 21 years. The variety of underlying diagnoses dictates a flexible approach to diagnosis and treatment that is tailored to the particular aetiology. The aim of diagnosis should be to uncover any potentially treatable causes. At a minimum, these patients should have brain imaging, preferably MRI, serum ceruloplasmin and 24-hour urinary copper testing to rule out Wilson's disease, and a levodopa trial to rule out dopa-responsive dystonia. Further investigation could include genetic testing and/or various laboratory tests as discussed,

usually guided by hallmark clinical findings, for example, remarkably slowed saccadic eye movements suggesting spinocerebellar ataxia 2 or chorea in a parent suggesting Huntington's disease. The mainstay of treatment relies on medications used in idiopathic Parkinson's disease, with the goal of maximizing functional improvement and minimizing treatment-related complications.

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BAILES

EXHIBIT 16



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Alzheimer's
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Dementia

Alzheimer's Association Report

2015 Alzheimer's disease facts and figures

Alzheimer's Association*

Abstract

This report discusses the public health impact of Alzheimer's disease (AD), including incidence and prevalence, mortality rates, costs of care and the overall effect on caregivers and society. It also examines the challenges encountered by health care providers when disclosing an AD diagnosis to patients and caregivers. An estimated 5.3 million Americans have AD; 5.1 million are age ≥ 65 years, and approximately 200,000 are age < 65 years and have younger onset AD. By mid-century, the number of people living with AD in the United States is projected to grow by nearly 10 million, fueled in large part by the aging baby boom generation. Today, someone in the country develops AD every 67 seconds. By 2050, one new case of AD is expected to develop every 33 seconds, resulting in nearly 1 million new cases per year, and the estimated prevalence is expected to range from 11 million to 16 million. In 2013, official death certificates recorded 84,767 deaths from AD, making AD the sixth leading cause of death in the United States and the fifth leading cause of death in Americans age ≥ 65 years. Between 2000 and 2013, deaths resulting from heart disease, stroke and prostate cancer decreased 14%, 23% and 11%, respectively, whereas deaths from AD increased 71%. The actual number of deaths to which AD contributes (or deaths with AD) is likely much larger than the number of deaths from AD recorded on death certificates. In 2015, an estimated 700,000 Americans age ≥ 65 years will die with AD, and many of them will die from complications caused by AD. In 2014, more than 15 million family members and other unpaid caregivers provided an estimated 17.9 billion hours of care to people with AD and other dementias, a contribution valued at more than \$217 billion. Average per-person Medicare payments for services to beneficiaries age ≥ 65 years with AD and other dementias are more than two and a half times as great as payments for all beneficiaries without these conditions, and Medicaid payments are 19 times as great. Total payments in 2015 for health care, long-term care and hospice services for people age ≥ 65 years with dementia are expected to be \$226 billion. Among people with a diagnosis of AD or another dementia, fewer than half report having been told of the diagnosis by their health care provider. Though the benefits of a prompt, clear and accurate disclosure of an AD diagnosis are recognized by the medical profession, improvements to the disclosure process are needed. These improvements may require stronger support systems for health care providers and their patients.

Keywords:

Alzheimer's disease; Dementia; Diagnostic criteria; Prevalence; Incidence; Mortality; Morbidity; Caregivers; Family caregiver; Spouse caregiver; Sandwich generation caregiver; Health care costs; Health care expenditures; Long-term care costs; Medicare spending; Medicaid spending; Disclosure awareness; Disclosure practices; Medicare Current Beneficiary Survey (MCBS); Activities of daily living (ADLs); Instrumental activities of daily living (IADLs)

1. About this report

2015 Alzheimer's Disease Facts and Figures is a statistical resource for U.S. data related to Alzheimer's disease, the most common cause of dementia, as well as other dementias. Background and context for interpretation of the data are

contained in the Overview. This information includes descriptions of the various causes of dementia and a summary of current knowledge about Alzheimer's disease. Additional sections address prevalence, mortality and morbidity, caregiving and use and costs of health care. The Special Report addresses issues surrounding the disclosure of an Alzheimer's diagnosis to individuals with the disease.

Specific information in this year's *Alzheimer's Disease Facts and Figures* includes:

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- Proposed criteria and guidelines for diagnosing Alzheimer's disease from the National Institute on Aging and the Alzheimer's Association.
- Overall number of Americans with Alzheimer's disease nationally and for each state.
- Proportion of women and men with Alzheimer's and other dementias.
- Estimates of lifetime risk for developing Alzheimer's disease.
- Number of deaths due to Alzheimer's disease nationally and for each state, and death rates by age.
- Number of family caregivers, hours of care provided, economic value of unpaid care nationally and for each state and the impact of caregiving on caregivers.
- Use and costs of health care, long-term care and hospice care for people with Alzheimer's disease and other dementias.
- Challenges surrounding the disclosure of an Alzheimer's disease diagnosis.

The Appendices detail sources and methods used to derive data in this report.

This report frequently cites statistics that apply to all individuals with dementia. When possible, specific information about individuals with Alzheimer's disease is provided; in other cases, the reference may be a more general one of "individuals with Alzheimer's disease and other dementias."

2. Overview of Alzheimer's disease

Alzheimer's disease is a degenerative brain disease and the most common cause of dementia [1,2]. Dementia is also caused by other diseases and conditions. It is characterized by a decline in memory, language, problem-solving and other cognitive skills that affects a person's ability to perform everyday activities. This decline occurs because nerve cells (neurons) in parts of the brain involved in cognitive function have been damaged and no longer function normally. In Alzheimer's disease, neuronal damage eventually affects parts of the brain that enable a person to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-the-clock care. Alzheimer's disease is ultimately fatal.

2.1. Dementia

Physicians often refer to the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* to guide them in determining if an individual has dementia, and, if so, the condition causing dementia. The latest edition of the manual, *DSM-5*, classifies dementia as a neurocognitive disorder [3]. Dementia may be either a major or a mild neurocognitive disorder. To meet *DSM-5* criteria for a major neurocognitive disorder, an individual must have evidence of significant cognitive decline, and the decline must interfere with independence in everyday

activities (for example, assistance may be needed with complex activities such as paying bills or managing medications). To meet *DSM-5* criteria for a mild neurocognitive disorder, an individual must have evidence of modest cognitive decline, but the decline does not interfere with everyday activities (individuals can still perform complex activities such as paying bills or managing medications, but the activities require greater mental effort).

When an individual has these or other symptoms of dementia, a physician must conduct tests to identify the cause. Different causes of dementia are associated with distinct symptom patterns and brain abnormalities, as described in Table 1. Increasing evidence from long-term observational and autopsy studies indicates that many people with dementia, especially those in the older age groups, have brain abnormalities associated with more than one cause of dementia [5,6,8–10]. This is called mixed dementia.

In some cases, individuals do not have dementia, but instead have a condition whose symptoms mimic those of dementia. Common causes of dementia-like symptoms are depression, delirium, side effects from medications, thyroid problems, certain vitamin deficiencies and excessive use of alcohol. Unlike dementia, these conditions often may be reversed with treatment. One meta-analysis, a method of analysis in which results of multiple studies are examined, reported that 9 percent of people with dementia-like symptoms did not in fact have dementia, but had other conditions that were potentially reversible [11].

2.2. Alzheimer's disease

Alzheimer's disease was first identified more than 100 years ago, but 70 years passed before it was recognized as the most common cause of dementia and a "major killer" [12]. Although research has revealed a great deal about Alzheimer's, much is yet to be discovered about the precise biologic changes that cause Alzheimer's, why it progresses more quickly in some than in others, and how the disease can be prevented, slowed or stopped.

Researchers believe that early detection will be key to preventing, slowing and stopping Alzheimer's disease. The last 10 years have seen a tremendous growth in research on early detection. This research spurred the 2011 publication of proposed new diagnostic criteria and guidelines for Alzheimer's disease [13–16]. Under the proposed criteria, the disease begins before symptoms such as memory loss appear, while earlier criteria require memory loss and a decline in thinking abilities for an Alzheimer's diagnosis to be made. Because scientific evaluation of the proposed criteria is ongoing, "Alzheimer's disease" in this report refers to the disease as defined by the earlier criteria [17].

2.2.1. Symptoms

Alzheimer's disease symptoms vary among individuals. The most common initial symptom is a gradually worsening ability to remember new information. This memory decline

Table 1
Causes and characteristics of dementia*

Cause	Characteristics
Alzheimer's disease	<p>Most common cause of dementia; accounts for an estimated 60 percent to 80 percent of cases. About half of these cases involve solely Alzheimer's pathology; many have evidence of pathologic changes related to other dementias. This is called mixed dementia (see mixed dementia in this table).</p> <p>Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavior changes and, ultimately, difficulty speaking, swallowing and walking. Revised criteria and guidelines for diagnosing Alzheimer's were proposed and published in 2011. They recommend that Alzheimer's be considered a slowly progressive brain disease that begins well before clinical symptoms emerge.</p> <p>The hallmark pathologies of Alzheimer's are the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are eventually accompanied by the damage and death of neurons.</p>
Vascular dementia	<p>Previously known as multi-infarct or post-stroke dementia, vascular dementia is less common as a sole cause of dementia than Alzheimer's, accounting for about 10 percent of dementia cases. However, it is very common in older individuals with dementia, with about 50 percent having pathologic evidence of vascular dementia (infarcts). In most cases, the infarcts coexist with Alzheimer's pathology (see mixed dementia in this table) [4].</p> <p>Impaired judgment or impaired ability to make decisions, plan or organize is more likely to be the initial symptom, as opposed to the memory loss often associated with the initial symptoms of Alzheimer's.</p> <p>Vascular dementia occurs most commonly from blood vessel blockage or damage leading to infarcts (strokes) or bleeding in the brain. The location, number and size of the brain injuries determine whether dementia will result and how the individual's thinking and physical functioning will be affected.</p> <p>In the past, evidence of vascular dementia was used to exclude a diagnosis of Alzheimer's (and vice versa). That practice is no longer considered consistent with the pathologic evidence, which shows that the brain changes of Alzheimer's and vascular dementia commonly coexist. When evidence of two or more causes of dementia are present at the same time, the individual is considered to have mixed dementia (see mixed dementia in this table).</p>
Dementia with Lewy bodies (DLB)	<p>People with DLB have some of the symptoms common in Alzheimer's, but are more likely to have initial or early symptoms of sleep disturbances, well-formed visual hallucinations and slowness, gait imbalance or other parkinsonian movement features. These features, as well as early visuospatial impairment, may occur in the absence of significant memory impairment.</p> <p>Lewy bodies are abnormal aggregations (or clumps) of the protein alpha-synuclein that accumulate in neurons. When they develop in a part of the brain called the cortex, dementia can result. Alpha-synuclein also aggregates in the brains of people with Parkinson's disease (PD), in which it is accompanied by severe neuronal loss in a part of the brain called the substantia nigra. While people with DLB and PD both have Lewy bodies, the onset of the disease is marked by motor impairment in PD and cognitive impairment in DLB.</p> <p>The brain changes of DLB alone can cause dementia. But very commonly brains with DLB have coexisting Alzheimer's pathology. In people with both DLB and Alzheimer's pathology, symptoms of both diseases may emerge and lead to some confusion in diagnosis. Vascular dementia can also coexist and contribute to the dementia. When evidence of more than one dementia is present, the individual is said to have mixed dementia (see mixed dementia in this table).</p>
Frontotemporal lobar degeneration (FTLD)	<p>Includes dementias such as behavioral-variant FTLD, primary progressive aphasia. Pick's disease, corticobasal degeneration and progressive supranuclear palsy.</p> <p>Typical early symptoms include marked changes in personality and behavior and difficulty with producing or comprehending language. Unlike Alzheimer's, memory is typically spared in the early stages of disease. Nerve cells in the front (frontal lobe) and side regions (temporal lobes) of the brain are especially affected, and these regions become markedly atrophied (shrunken). In addition, the upper layers of the cortex typically become soft and spongy and have protein inclusions (usually tau protein or the transactive response DNA-binding protein).</p> <p>The brain changes of behavioral-variant FTLD may occur in those age 65 years and older, similar to Alzheimer's disease, but most people with this form of dementia develop symptoms at a younger age (at about age 60). In this younger age group, FTLD is the second most common degenerative dementia.</p>
Mixed dementia	<p>Characterized by the hallmark abnormalities of more than one cause of dementia — most commonly Alzheimer's combined with vascular dementia, followed by Alzheimer's with DLB, and Alzheimer's with vascular dementia and DLB. Vascular dementia with DLB is much less common [5,6].</p> <p>Recent studies suggest that mixed dementia is more common than previously recognized, with about half of those with dementia having pathologic evidence of more than one cause of dementia [5,6].</p>
Parkinson's disease (PD) dementia	<p>Problems with movement (slowness, rigidity, tremor and changes in gait) are common symptoms of PD. In PD, alpha-synuclein aggregates appear in an area deep in the brain called the substantia nigra. The aggregates are thought to cause degeneration of the nerve cells that produce dopamine.</p> <p>The incidence of PD is about one-tenth that of Alzheimer's.</p> <p>As PD progresses, it often results in dementia secondary to the accumulation of Lewy bodies in the cortex (similar to DLB) or the accumulation of beta-amyloid clumps and tau tangles (similar to Alzheimer's disease).</p>

(Continued)

Table 1
Causes and characteristics of dementia* (Continued)

Cause	Characteristics
Creutzfeldt-Jakob disease	This very rare and rapidly fatal disorder impairs memory and coordination and causes behavior changes. Results from a misfolded protein (prion) that causes other proteins throughout the brain to misfold and malfunction. May be hereditary (caused by a gene that runs in one's family), sporadic (unknown cause) or caused by a known prion infection. A specific form called variant Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease.
Normal pressure hydrocephalus	Symptoms include difficulty walking, memory loss and inability to control urination. Accounts for less than 5 percent of dementia cases [7]. Caused by impaired reabsorption of cerebrospinal fluid and the consequent build-up of fluid in the brain, increasing pressure in the brain. People with a history of brain hemorrhage (particularly subarachnoid hemorrhage) and meningitis are at increased risk. Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid.

*For more information on these and other causes of dementia, visit alz.org/dementia.

occurs because the first neurons to malfunction and die are usually neurons in brain regions involved in forming new memories. As neurons in other parts of the brain malfunction and die, individuals experience other difficulties. The following are common symptoms of Alzheimer's:

- Memory loss that disrupts daily life.
- Challenges in planning or solving problems.
- Difficulty completing familiar tasks at home, at work or at leisure.
- Confusion with time or place.
- Trouble understanding visual images and spatial relationships.
- New problems with words in speaking or writing.
- Misplacing things and losing the ability to retrace steps.
- Decreased or poor judgment.
- Withdrawal from work or social activities.
- Changes in mood and personality, including apathy and depression.

For more information about the symptoms of Alzheimer's, visit alz.org.

The pace at which symptoms advance from mild to moderate to severe varies from person to person. As the disease progresses, cognitive and functional abilities decline. People need help with basic activities of daily living, such as bathing, dressing, eating and using the bathroom; lose their ability to communicate; fail to recognize loved ones; and become bed-bound and reliant on around-the-clock care. When individuals have difficulty moving, they are more vulnerable to infections, including pneumonia (infection of the lungs). Alzheimer's-related pneumonia is often a contributing factor to the death of people with Alzheimer's disease.

2.2.2. Changes in the brain that are associated with Alzheimer's disease

A healthy adult brain has about 100 billion neurons, each with long, branching extensions. These extensions enable indi-

vidual neurons to form connections with other neurons. At such connections, called synapses, information flows in tiny bursts of chemicals that are released by one neuron and detected by a receiving neuron. The brain contains about 100 trillion synapses. They allow signals to travel rapidly through the brain's neuronal circuits, creating the cellular basis of memories, thoughts, sensations, emotions, movements and skills.

The accumulation of the protein beta-amyloid (called beta-amyloid plaques) *outside* neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) *inside* neurons are two of several brain changes believed to contribute to the development of Alzheimer's. In Alzheimer's disease, information transfer at synapses begins to fail, the number of synapses declines, and neurons eventually die. The accumulation of beta-amyloid is believed to interfere with the neuron-to-neuron communication at synapses and to contribute to cell death. Tau tangles block the transport of nutrients and other essential molecules inside neurons and are also believed to contribute to cell death. The brains of people with advanced Alzheimer's show dramatic shrinkage from cell loss and widespread debris from dead and dying neurons.

The brain changes associated with Alzheimer's may begin 20 or more years [18–20] before symptoms appear. The time between the initial brain changes of Alzheimer's and the symptoms of advanced Alzheimer's is considered by scientists to represent the "continuum" of Alzheimer's. At the start of the continuum, individuals are able to function normally despite these brain changes. Further along the continuum, the brain can no longer compensate for the neuronal damage that has occurred, and individuals show subtle decline in cognitive function. Later, neuronal damage is so significant that individuals show obvious cognitive decline, including symptoms such as memory loss or confusion as to time or place. Later still, basic bodily functions such as swallowing are impaired.

2.2.3. Genetic mutations that cause Alzheimer's disease

A small percentage of Alzheimer's cases (an estimated 1 percent or less) [21] develop as a result of mutations to

any of three specific genes. A genetic mutation is an abnormal change in the sequence of chemical pairs that make up genes. These mutations involve the gene for the amyloid precursor protein (APP) and the genes for the presenilin 1 and presenilin 2 proteins. Those inheriting a mutation to the APP or presenilin 1 genes are guaranteed to develop Alzheimer's. Those inheriting a mutation in the presenilin 2 gene have a 95 percent chance of developing the disease [22]. Individuals with mutations in any of these three genes tend to develop Alzheimer's symptoms before age 65, sometimes as early as age 30, while the vast majority of individuals with Alzheimer's have late-onset disease, occurring at age 65 or later.

2.2.4. Risk factors for Alzheimer's disease

With the exception of the rare cases of Alzheimer's caused by genetic mutations, experts believe that Alzheimer's, like other common chronic diseases, develops as a result of multiple factors rather than a single cause. This section describes known risk factors for Alzheimer's. Other factors that may affect risk are being studied.

2.2.4.1. Age

The greatest risk factor for Alzheimer's disease is age. Most people with Alzheimer's disease are diagnosed at age 65 or older. People younger than 65 can also develop the disease, although this is much more rare (see the Prevalence section). While age is the greatest risk factor, Alzheimer's is not a normal part of aging and age alone is not sufficient to cause the disease.

2.2.4.2. Apolipoprotein E (APOE) $\epsilon 4$ gene

The APOE gene provides the blueprint for a protein that transports cholesterol in the bloodstream. Everyone inherits one form of the APOE gene— $\epsilon 2$, $\epsilon 3$ or $\epsilon 4$ —from each parent:

- The $\epsilon 3$ form is the most common [23], with about 60 percent of the U.S. population inheriting $\epsilon 3$ from both parents [24].
- The $\epsilon 4$ form is carried by an estimated 20 to 30 percent of individuals; approximately 2 percent of the U.S. population has two copies of $\epsilon 4$ [23,24].
- The $\epsilon 2$ form is carried by an estimated 10 to 20 percent of the population [23,24].

Having the $\epsilon 4$ form increases one's risk compared with having the $\epsilon 3$ form, while having the $\epsilon 2$ form may decrease one's risk compared with the $\epsilon 3$ form. Those who inherit one copy of the $\epsilon 4$ form have a three-fold higher risk of developing Alzheimer's than those without the $\epsilon 4$ form, while those who inherit two copies of the $\epsilon 4$ form have an 8- to 12-fold higher risk [25,26]. In addition, those with the $\epsilon 4$ form are more likely to develop Alzheimer's at a younger age than those with the $\epsilon 2$ or $\epsilon 3$ forms of the APOE gene [27]. Researchers estimate that between 40 and 65 percent of people diagnosed with Alzheimer's have one or two copies of the APOE $\epsilon 4$ gene [23,28,29].

Unlike inheriting a genetic mutation that causes Alzheimer's, inheriting the $\epsilon 4$ form of the APOE gene does not guarantee that an individual will develop Alzheimer's. This is also true for more than 20 recently identified genes that appear to affect the risk of Alzheimer's. These recently identified genes are believed to have a limited overall effect in the population because they are rare or only slightly increase risk [30].

2.2.4.3. Family history

A family history of Alzheimer's is not necessary for an individual to develop the disease. However, individuals who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than those who do not have a first-degree relative with Alzheimer's [25,31]. Those who have more than one first-degree relative with Alzheimer's are at even higher risk [32]. When diseases run in families, heredity (genetics), shared environmental and lifestyle factors, or both, may play a role. The increased risk associated with having a family history of Alzheimer's is not entirely explained by whether the individual has inherited the APOE $\epsilon 4$ risk gene.

2.2.4.4. Mild cognitive impairment (MCI)

MCI is a condition in which an individual has mild but measurable changes in thinking abilities that are noticeable to the person affected and to family members and friends, but do not affect the individual's ability to carry out everyday activities. People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's and other dementias than people without MCI. Revised criteria and guidelines for diagnosis of Alzheimer's disease published in 2011 [13–16] suggest that in some cases MCI is actually an early stage of Alzheimer's or another dementia. However, MCI does not always lead to dementia. In some individuals, MCI reverts to normal cognition or remains stable. In other cases, such as when a medication causes cognitive impairment, MCI is mistakenly diagnosed. Therefore, it's important that people experiencing cognitive impairment seek help as soon as possible for diagnosis and possible treatment.

2.2.4.5. Cardiovascular disease risk factors

Growing evidence suggests that the health of the brain is closely linked to the overall health of the heart and blood vessels. The brain is nourished by one of the body's richest networks of blood vessels. A healthy heart helps ensure that enough blood is pumped through these blood vessels, and healthy blood vessels help ensure that the brain is supplied with the oxygen- and nutrient-rich blood it needs to function normally.

Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of dementia. These factors include smoking [33–35], obesity in midlife [36–38] and diabetes [35,39–42]. Some evidence suggests that impaired glucose processing (a precursor to diabetes) may

also result in an increased risk for dementia [36,43,44]. Growing evidence also implicates midlife hypertension [36,45–47] and midlife high cholesterol [48,49] as risk factors.

Conversely, factors that protect the heart may also protect the brain and reduce the risk of developing Alzheimer's and other dementias. Physical activity [42,50,51] appears to be one of these factors. In addition, emerging evidence suggests that consuming a diet that benefits the heart, such as one that is low in saturated fats and rich in vegetables and fruits, may be associated with reduced Alzheimer's and dementia risk [42,52–54].

Unlike genetic risk factors, many cardiovascular disease risk factors are *modifiable*—that is, they can be changed to decrease the likelihood of developing cardiovascular disease and, possibly, Alzheimer's and other forms of dementia.

Researchers have begun to study combinations of health factors and lifestyle behaviors to learn whether they are better than individual factors and behaviors at identifying increased risk [55].

2.2.4.6. Education

People with fewer years of formal education are at higher risk for Alzheimer's and other dementias than those with more years of formal education [56–60]. Some researchers believe that having more years of education builds a “cognitive reserve” that enables individuals to better compensate for changes in the brain that could result in symptoms of Alzheimer's or another dementia [59,61,62]. According to the cognitive reserve hypothesis, having more years of education increases the connections between neurons in the brain and enables the brain to compensate for the early brain changes of Alzheimer's by using alternate routes of neuron-to-neuron communication to complete a cognitive task.

Some scientists believe other factors may contribute to or explain the increased risk of dementia among those with lower educational attainment. These factors include being more likely to have occupations that are less mentally stimulating [63]. In addition, lower educational attainment may reflect lower socioeconomic status [63], which may increase one's likelihood of poor nutrition and decrease one's ability to afford health care or obtain suggested treatments.

2.2.4.7. Social and cognitive engagement

Additional studies suggest that remaining socially and mentally active throughout life may support brain health and possibly reduce the risk of Alzheimer's and other dementias [64–76]. Remaining socially and mentally active may help build cognitive reserve, but the exact mechanism by which this may occur is unknown. More research is needed to better understand how social and cognitive engagement may affect biological processes to reduce risk.

2.2.4.8. Traumatic brain injury (TBI)

Moderate and severe TBIs increase the risk of developing Alzheimer's disease and other dementias [77]. TBI is the

disruption of normal brain function caused by a blow or jolt to the head or penetration of the skull by a foreign object. Not all blows or jolts to the head disrupt brain function. Moderate TBI is defined as a head injury resulting in loss of consciousness or post-traumatic amnesia that lasts more than 30 minutes. If loss of consciousness or post-traumatic amnesia lasts more than 24 hours, the injury is considered severe. Half of all moderate and severe TBIs are caused by motor vehicle accidents [78]. Moderate TBI is associated with twice the risk of developing Alzheimer's and other dementias compared with no head injuries, and severe TBI is associated with 4.5 times the risk [79].

Individuals who have experienced repeated head injuries, such as boxers, football players and combat veterans, are at higher risk of dementia, cognitive impairment and neurodegenerative disease than individuals who have not experienced head injury [80–86]. Evidence suggests that even repeated mild TBI might promote neurodegenerative disease [87–89]. Some of these neurodegenerative diseases, such as chronic traumatic encephalopathy, can only be distinguished from Alzheimer's upon autopsy.

2.2.5. Diagnosis

A diagnosis of Alzheimer's disease is most commonly made by an individual's primary care physician. No single, simple test exists to diagnose Alzheimer's disease. A variety of approaches and tools are available to help make a diagnosis. They include the following:

- Obtaining a medical and family history from the individual, including psychiatric history and history of cognitive and behavioral changes.
- Asking a family member or other person close to the individual to provide input about changes in thinking skills or behavior.
- Seeking input from a specialist, such as a neurologist.
- Conducting cognitive tests and physical and neurologic examinations.
- Having the individual undergo a magnetic resonance imaging (MRI) scan, which can help identify brain changes, such as a tumor, that could explain the individual's symptoms.

Before making a diagnosis of Alzheimer's, physicians may refer to medical resources such as the *DSM-5* and published diagnostic criteria that delve even further into the disease.

2.2.6. Treatment of Alzheimer's disease

2.2.6.1. Pharmacologic treatment

Pharmacologic treatments employ medication to slow or stop an illness or treat its symptoms. Six drugs have been approved by the U.S. Food and Drug Administration (FDA) that temporarily improve symptoms of Alzheimer's disease by increasing the amount of chemicals called neurotransmitters in the brain. The effectiveness of these drugs

varies from person to person. However, none of the treatments available today for Alzheimer's disease slows or stops the damage to neurons that causes Alzheimer's symptoms and eventually makes the disease fatal.

In December 2014, the FDA approved the sixth drug, which combines two existing FDA-approved Alzheimer's drugs and is for moderate to severe disease. Prior to that, the last approval of an Alzheimer's drug was in 2003. In the decade of 2002–2012, 244 drugs for Alzheimer's were tested in clinical trials registered with clinicaltrials.gov, a National Institutes of Health registry of publicly and privately funded clinical studies [90]. The drug approved in 2003 was the only drug of the 244 tested to complete the clinical trials process and receive approval. Many factors contribute to the difficulty of developing effective treatments for Alzheimer's. These factors include the high cost of drug development, the relatively long time needed to observe disease progression in Alzheimer's, and the structure of the brain, which is protected by the blood-brain barrier, through which few drugs can cross.

2.2.6.2. Non-pharmacologic therapy

Non-pharmacologic therapies are those that employ approaches other than medication, such as music therapy and reminiscence therapy (therapy in which photos and other familiar items may be used to elicit recall). As with current pharmacologic therapies, non-pharmacologic therapies have not been shown to alter the course of Alzheimer's disease.

Non-pharmacologic therapies are often used with the goal of maintaining or improving cognitive function, the ability to perform activities of daily living, or overall quality of life. They also may be used with the goal of reducing behavioral symptoms such as depression, apathy, wandering, sleep disturbances, agitation and aggression.

Systematic reviews of published research on non-pharmacologic therapies have found that some, such as exercise and cognitive activity (for example, gardening, word games, listening to music and cooking) show promise [91]. However, few non-pharmacologic therapies have been tested in randomized controlled studies, which provide the strongest evidence of whether a therapy is effective. In randomized controlled studies, participants are randomly assigned to receive a therapy or not receive a therapy, and results from the two groups are compared. Additional research on non-pharmacologic therapies is needed to better evaluate their effectiveness.

2.2.7. Living with Alzheimer's disease

Despite the lack of disease-modifying therapies for Alzheimer's, studies have consistently shown that active management of Alzheimer's and other dementias can improve quality of life through all stages of the disease for individuals with dementia and their caregivers [92–94]. Active management includes:

- (1) appropriate use of available treatment options,
- (2) effective management of coexisting conditions,

- (3) coordination of care among physicians, other health care professionals and lay caregivers,
- (4) participation in activities and/or adult day care programs and
- (5) taking part in support groups and supportive services.

To learn more about each of these ways of helping to manage Alzheimer's, as well as practical information for living with the disease and being a caregiver for an individual with Alzheimer's, visit alz.org.

2.2.8. A modern diagnosis of Alzheimer's disease: Proposed criteria and guidelines

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised criteria and guidelines for diagnosing Alzheimer's disease [13–16]. These criteria and guidelines updated diagnostic criteria and guidelines published in 1984 by the National Institute of Neurological Disorders and Stroke and the Alzheimer's Association [17]. In 2012, the NIA and the Alzheimer's Association also proposed new guidelines to help pathologists describe and categorize the brain changes associated with Alzheimer's disease and other dementias on autopsy [95].

It is important to note that more research is needed before the proposed diagnostic criteria and guidelines can be used in clinical settings, such as in a doctor's office.

2.2.8.1. Differences between the original and proposed criteria

The 1984 diagnostic criteria and guidelines were based chiefly on a doctor's clinical judgment about the cause of an individual's symptoms, taking into account reports from the individual, family members and friends; results of cognitive tests; and general neurological assessment. The new criteria and guidelines incorporate two notable changes:

- (1) They identify three stages of Alzheimer's disease, with the first occurring before symptoms such as memory loss develop. In contrast, for Alzheimer's disease to be diagnosed using the 1984 criteria, memory loss and a decline in thinking abilities must have already occurred.
- (2) They incorporate biomarker tests. A biomarker is a biological factor that can be measured to indicate the presence or absence of disease, or the risk of developing a disease. For example, blood glucose level is a biomarker of diabetes, and cholesterol level is a biomarker of heart disease risk. Levels of certain proteins in fluid (for example, levels of beta-amyloid and tau in the cerebrospinal fluid and the presence of particular groups of proteins in blood) are among several factors being studied as possible biomarkers for Alzheimer's. Finding a simple and inexpensive test, such as a blood test, would be ideal for patients, physicians and scientists. Research is underway to develop such a test, but no test to date has shown the accuracy and reliability needed to diagnose Alzheimer's.

2.2.8.2. *The three stages of Alzheimer's disease proposed by the 2011 criteria and guidelines*

The three stages of Alzheimer's disease proposed by the 2011 criteria and guidelines are preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease. An individual who does not yet have outward symptoms of Alzheimer's but does have some of the early brain changes of Alzheimer's (as detected by brain imaging and other biomarker tests) would be said to have preclinical Alzheimer's disease. Those who have very mild symptoms but can still perform everyday tasks would be described as having MCI due to Alzheimer's. Individuals whose symptoms are more pronounced and interfere with carrying out everyday tasks would be said to have dementia due to Alzheimer's disease.

2.2.8.2.1. *Preclinical Alzheimer's disease*

In this stage, individuals have measurable changes in the brain, cerebrospinal fluid and/or blood (biomarkers) that indicate the earliest signs of disease, but they have not yet developed noticeable symptoms such as memory loss. This preclinical or presymptomatic stage reflects current thinking that Alzheimer's-related brain changes may begin 20 years or more before symptoms occur [18–20]. Although the 2011 criteria and guidelines identify preclinical disease as a stage of Alzheimer's, they do not establish diagnostic criteria that doctors can use now. Rather, they state that additional research is needed before this stage of Alzheimer's can be identified.

2.2.8.2.2. *MCI due to Alzheimer's disease*

Individuals with MCI have mild but measurable changes in thinking abilities that are noticeable to the person affected and to family members and friends, but that do not affect the individual's ability to carry out everyday activities. Studies indicate that as many as 10 to 20 percent of people age 65 or older have MCI [96–98]. Among people whose MCI symptoms cause them enough concern to contact their physicians for an exam, as many as 15 percent progress from MCI to dementia each year. Nearly half of all people who have visited a doctor about MCI symptoms will develop dementia in 3 or 4 years [99].

When individuals in a community are assessed, regardless of whether they have memory or cognitive complaints, the estimated percentage who will progress from MCI to Alzheimer's is slightly lower—up to 10 percent per year [100]. Further cognitive decline is more likely among individuals whose MCI involves memory problems than among those whose MCI does not involve memory problems. Over a year, most individuals with MCI who are identified through community sampling remain cognitively stable. Some, primarily those without memory problems, experience an improvement in cognition or revert to normal cognitive status [101]. It is unclear why some people with MCI develop dementia and others do not.

After accurate and reliable biomarker tests for Alzheimer's have been identified, the 2011 criteria and guidelines recommend biomarker testing for people with MCI to learn whether they have biological changes that put them at high risk of developing Alzheimer's disease or another dementia. If testing shows that changes in the brain, cerebrospinal fluid and/or blood are similar to the changes of Alzheimer's, the proposed criteria and guidelines recommend a diagnosis of MCI due to Alzheimer's disease. However, this diagnosis cannot currently be made, as additional research is needed to validate the 2011 criteria before they can be used in clinical settings.

2.2.8.2.3. *Dementia due to Alzheimer's disease*

This stage, as described by the 2011 diagnostic criteria and guidelines, is characterized by quite noticeable memory, thinking and behavioral symptoms that, unlike MCI, impair a person's ability to function in daily life.

2.2.8.3. *Biomarker tests*

The 2011 criteria and guidelines identify two biomarker categories: (1) biomarkers showing the level of beta-amyloid accumulation in the brain and (2) biomarkers showing that neurons in the brain are injured or actually degenerating.

Many researchers believe that future treatments to slow or stop the progression of Alzheimer's disease and preserve brain function (called “disease-modifying” treatments) will be most effective when administered during the preclinical and MCI stages of the disease. Biomarker tests will be essential to identify which individuals are in these early stages and should receive disease-modifying treatment. They also will be critical for monitoring the effects of treatment. At this time, however, more research is needed to validate the accuracy of biomarkers and better understand which biomarker test or combination of tests is most effective in diagnosing Alzheimer's disease. The most effective test or combination of tests may differ depending on the stage of the disease and the cause of dementia [102].

2.2.8.4. *Progress toward implementing criteria and validating biomarkers*

Since the revised criteria were published in 2011, dozens of scientists have published results of studies implementing the revised criteria in research settings, examining the accuracy of biomarker tests in detecting and predicting Alzheimer's, and using biomarker tests to distinguish Alzheimer's from other forms of dementia. Although additional studies are needed before the revised criteria and guidelines are ready for use in physicians' offices, preliminary evidence supporting the revised criteria and biomarker tests is growing [103–119].

3. Prevalence

Millions of Americans have Alzheimer's disease and other dementias. The number of Americans with Alzheimer's disease and other dementias will grow each year

as the size and proportion of the U.S. population age 65 and older continue to increase. The number will escalate rapidly in coming years as the baby boom generation ages.

The prevalence of Alzheimer's disease refers to the proportion of people in a population who have Alzheimer's at a given point in time. This section reports on the number and proportion of people with Alzheimer's disease to describe the magnitude of the burden of Alzheimer's on the community and the health care system. Incidence, the number of new cases per year, is also provided as an estimate of the risk of developing Alzheimer's disease and other dementias for different age groups. Estimates from selected studies on the number and proportion of people with Alzheimer's and other dementias vary depending on how each study was conducted. Data from several studies are used in this section.

3.1. Prevalence of Alzheimer's disease and other dementias in the United States

An estimated 5.3 million Americans of all ages have Alzheimer's disease in 2015. This number includes an estimated 5.1 million people age 65 and older [120],^{A1} and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's [121].

- One in nine people age 65 and older (11 percent) has Alzheimer's disease.^{A2}
- About one-third of people age 85 and older (32 percent) have Alzheimer's disease [120].
- Eighty-one percent of people who have Alzheimer's disease are age 75 or older (Fig. 1) [120].^{A3}

The estimated number of individuals age 65 and older with Alzheimer's disease comes from a recent study using the latest data from the 2010 U.S. Census and the Chicago Health and Aging Project (CHAP), a population-based study of chronic health diseases of older people [120].

National estimates of the prevalence of all forms of dementia are not available from CHAP, but are available from other population-based studies including the Aging, Demographics, and Memory Study (ADAMS), a nationally

representative sample of older adults [122,123]^{A4}. Based on estimates from ADAMS, 14 percent of people age 71 and older in the United States have dementia [122].

Prevalence studies such as CHAP and ADAMS are designed so that everyone in the study is tested for dementia. But in the community, only about half of those who would meet the diagnostic criteria for Alzheimer's disease and other dementias are diagnosed with dementia by a physician [124,125]. Because Alzheimer's disease is underdiagnosed, half of the estimated 5.3 million Americans with Alzheimer's may not have been told by a physician that they have it.

3.1.1. Preclinical Alzheimer's disease

The estimates of the number and proportion of people who have Alzheimer's are based on commonly accepted criteria for diagnosing Alzheimer's disease that have been used since 1984. These criteria are applicable only after the onset of symptoms. But as described in the Overview, revised criteria and guidelines by the National Institute on Aging and the Alzheimer's Association published in 2011 [13–16] propose that Alzheimer's begins before the onset of symptoms, which aligns with what most researchers now believe. The 2011 criteria identify three stages of Alzheimer's disease: preclinical Alzheimer's, mild cognitive impairment (MCI) due to Alzheimer's and dementia due to Alzheimer's. Because more research is needed to validate tests for detecting preclinical Alzheimer's and MCI due to Alzheimer's, the number of people in these stages is difficult to estimate. However, if Alzheimer's disease could be detected before symptoms developed, the number of people reported to have Alzheimer's disease would be much larger than what is presented in this report.

3.1.2. Subjective cognitive decline

The experience of worsening or more frequent confusion or memory loss (often referred to as subjective cognitive decline) is one of the earliest warning signs of Alzheimer's disease and may be a way to identify people who are at high risk of developing Alzheimer's and other dementias as well as MCI [126,127]. Subjective cognitive decline does not refer to someone occasionally forgetting their keys or the name of someone they recently met; it refers to more serious issues such as having trouble remembering how to do things they have always done or forgetting things that they would normally know. Not all of those who experience subjective cognitive decline go on to develop MCI or Alzheimer's disease and other dementias, but many do [128]. Data from the 2012 Behavioral Risk Factor Surveillance System (BRFSS) survey, which included questions on self-perceived confusion and memory loss for 21 states, showed that 13 percent of Americans age 45 and older reported experiencing worsening confusion or memory loss, but 77 percent had not consulted a health care professional about it [129]. Individuals concerned about declines in memory and other

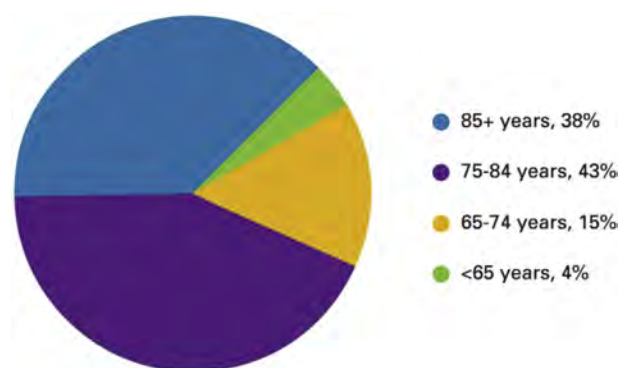


Fig. 1. Ages of people with Alzheimer's disease in the United States, 2015. Created from data from Hebert and colleagues [120].^{A3}

cognitive abilities should consult a health care professional.

3.1.3. Differences between women and men in the prevalence of Alzheimer's disease and other dementias

More women than men have AD and other dementias. Almost two-thirds of Americans with Alzheimer's are women [120].^{A5} Of the 5.1 million people age 65 and older with Alzheimer's in the United States, 3.2 million are women and 1.9 million are men [120].^{A5} Based on estimates from ADAMS, among people age 71 and older, 16 percent of women have Alzheimer's disease and other dementias compared with 11 percent of men [122,130].

There are a number of potential reasons why more women than men have Alzheimer's disease and other dementias. The prevailing view has been that this discrepancy is due to the fact that women live longer than men on average, and older age is the greatest risk factor for Alzheimer's [130,131]. Many studies of incidence (which indicates risk of developing disease) of Alzheimer's [57,58,131–135] or any dementia [56,57,132,133,136] have found no significant difference between men and women in the proportion who develop Alzheimer's or other dementias at any given age. However, limited new research suggests that risk could be higher for women, potentially due to biological or genetic variations or even different life experiences (for example, type and amount of education, or occupational choices) [137]. Data from the Framingham Study suggests that because men have a higher rate of death from cardiovascular disease than women in middle age, men who survive beyond age 65 may have a healthier cardiovascular risk profile and thus a lower risk for dementia than women of the same age, though more research is needed to support this finding [138]. Another large study showed that the *APOE* ϵ 4 genotype, the best known genetic risk factor for Alzheimer's disease, may have a stronger association with Alzheimer's disease in women than men [139,140]. It is unknown why this may be the case, but some evidence suggests an interaction between the *APOE* ϵ 4 genotype and the sex hormone estrogen [141,142]. Finally, because low education is a risk factor for dementia [50–60], it is possible that lower educational attainment in women than in men born in the first half of the 20th century could account for a higher risk of Alzheimer's and other dementias in women; however, this possibility has not been thoroughly investigated scientifically.

3.1.4. Racial and ethnic differences in the prevalence of Alzheimer's disease and other dementias

Although there are more non-Hispanic whites living with Alzheimer's and other dementias than any other racial or ethnic group in the United States, older African-Americans and Hispanics are more likely than older whites to have Alz-

heimer's disease and other dementias [143,144]. A review of many studies by an expert panel concluded that older African-Americans are about twice as likely to have Alzheimer's and other dementias as older whites [145,146], and Hispanics are about one and one-half times as likely to have Alzheimer's and other dementias as older whites [146,147].^{A6}

Variations in health, lifestyle and socioeconomic risk factors across racial groups likely account for most of the differences in risk of Alzheimer's disease and other dementias by race. Despite some evidence that the influence of genetic risk factors on Alzheimer's and other dementias may differ by race [148], genetic factors do not appear to account for the large prevalence differences among racial groups [149,150]. Instead, health conditions such as cardiovascular disease and diabetes, which increase risk for Alzheimer's disease and other dementias, are believed to account for these differences as they are more prevalent in African-American and Hispanic people. Lower levels of education and other socioeconomic characteristics in these communities may also increase risk. Some studies suggest that differences based on race and ethnicity do not persist in rigorous analyses that account for these factors [57,122].

There is evidence that missed diagnoses of Alzheimer's disease and other dementias are more common among older African-Americans and Hispanics than among older whites [151,152], but it is unclear whether disparities in missed diagnoses have lessened in recent years. Based on data for Medicare beneficiaries age 65 and older, Alzheimer's disease or another dementia had been diagnosed in 8 percent of white older adults, 11 percent of African-Americans and 12 percent of Hispanics [153]. Although rates of diagnosis were higher among African-Americans than among whites, according to prevalence studies that detect all people who have dementia irrespective of their use of the health care system, the rates should be twice as high (approximately 16 percent instead of 11 percent).

3.2. Estimates of the number of people with Alzheimer's disease by state

Table 2 lists the estimated number of people age 65 and older with Alzheimer's disease by state for 2015, the projected number for 2025, and the projected percentage change in the number of people with Alzheimer's between 2015 and 2025 [154].^{A7} Comparable estimates and projections for other causes of dementia are not available.

As shown in Fig. 2, between 2015 and 2025 every state and region across the country is expected to experience an increase of at least 14 percent in the number of people with Alzheimer's due to increases in the population age 65 and older. The West and Southeast are expected to experience the largest increases in numbers of people with

Table 2

Projections of total numbers of Americans age 65 and older with Alzheimer's by state

State	Projected number w/Alzheimer's (in thousands)		Percentage change 2015-2025
	2015	2025	
Alabama	87	110	26.4
Alaska	6.4	11	71.9
Arizona	120	200	66.7
Arkansas	53	67	26.4
California	590	840	42.4
Colorado	65	92	41.5
Connecticut	73	91	24.7
Delaware	17	23	35.3
District of Columbia	9.1	9	–1.1
Florida	500	720	44.0
Georgia	130	190	46.2
Hawaii	26	35	34.6
Idaho	23	33	43.5
Illinois	210	260	23.8
Indiana	110	130	18.2
Iowa	63	73	15.9
Kansas	51	62	21.6
Kentucky	68	86	26.5
Louisiana	82	110	34.1
Maine	26	35	34.6
Maryland	99	130	31.3
Massachusetts	120	150	25.0
Michigan	180	220	22.2
Minnesota	89	120	34.8
Mississippi	51	65	27.5
Missouri	110	130	18.2
Montana	19	27	42.1
Nebraska	33	40	21.2
Nevada	39	64	64.1
New Hampshire	22	32	45.5
New Jersey	170	210	23.5
New Mexico	36	53	47.2
New York	380	460	21.1
North Carolina	160	210	31.3
North Dakota	14	16	14.3
Ohio	210	250	19.0
Oklahoma	60	76	26.7
Oregon	60	84	40.0
Pennsylvania	270	320	18.5
Rhode Island	22	27	22.7
South Carolina	81	120	48.1
South Dakota	16	20	25.0
Tennessee	110	140	27.3
Texas	340	490	44.1
Utah	29	42	44.8
Vermont	12	17	41.7
Virginia	130	190	46.2
Washington	100	140	40.0
West Virginia	36	44	22.2
Wisconsin	110	130	18.2
Wyoming	8.8	13	47.7

NOTE. Created from data provided to the Alzheimer's Association by Weuve and colleagues [154].^{A7}

Alzheimer's between 2015 and 2025. These increases will have a marked impact on states' health care systems, as well as on families and caregivers.

3.3. Incidence of Alzheimer's disease

While prevalence is the number of *existing* cases of a disease in a population at a given time, incidence is the number of *new* cases of a disease that develop in a given period of time in a defined population—in this case, the U.S. population age 65 or older. Incidence provides a measure of *risk* for developing a disease. Approximately 473,000 people age 65 or older will develop Alzheimer's disease in the United States in 2015.^{A8} The number of new cases of Alzheimer's increases dramatically with age: in 2015, there will be approximately 61,000 new cases among people age 65 to 74, 172,000 new cases among people age 75 to 84, and 240,000 new cases among people age 85 and older (the “oldest-old”) [155].^{A8} This translates to approximately two new cases per 1000 people age 65 to 74, 13 new cases per 1000 people age 75 to 84, and 39 new cases per 1000 people age 85 and older.^{A8} Because of the increasing number of people age 65 and older in the United States, particularly the oldest-old, the annual number of new cases of Alzheimer's and other dementias is projected to double by 2050 [155].

- Every 67 seconds, someone in the United States develops Alzheimer's.^{A9}
- By mid-century, someone in the United States will develop the disease every 33 seconds.^{A9}

3.4. Lifetime risk of Alzheimer's disease

Lifetime risk is the probability that someone of a given age will develop a condition during his or her remaining lifespan. Data from the Framingham Study were used to estimate lifetime risks of Alzheimer's disease by age and sex [156].^{A10} As shown in Fig. 3, the study found that the estimated lifetime risk for Alzheimer's specifically at age 65 was one in six (17 percent) for women and one in 11 (9 percent) for men [156].

3.5. Trends in the prevalence and incidence of Alzheimer's disease

A growing number of studies indicate that the age-specific risk of Alzheimer's and other dementias in the United States and other higher-income Western countries may have declined in the past 25 years [157–164], though results are mixed [165]. These declines have largely been attributed to increasing levels of education and improved control of cardiovascular risk factors [159,166]. Such findings are promising and suggest that identifying and reducing risk factors for Alzheimer's and other dementias may be effective. Although these findings indicate that a person's risk of dementia at any given age may be decreasing slightly, it should be noted that the total number of Americans with Alzheimer's and other dementias is expected to continue to increase dramatically because of the population's shift to older ages (see Looking to the Future). Thus, while these findings are promising, they are

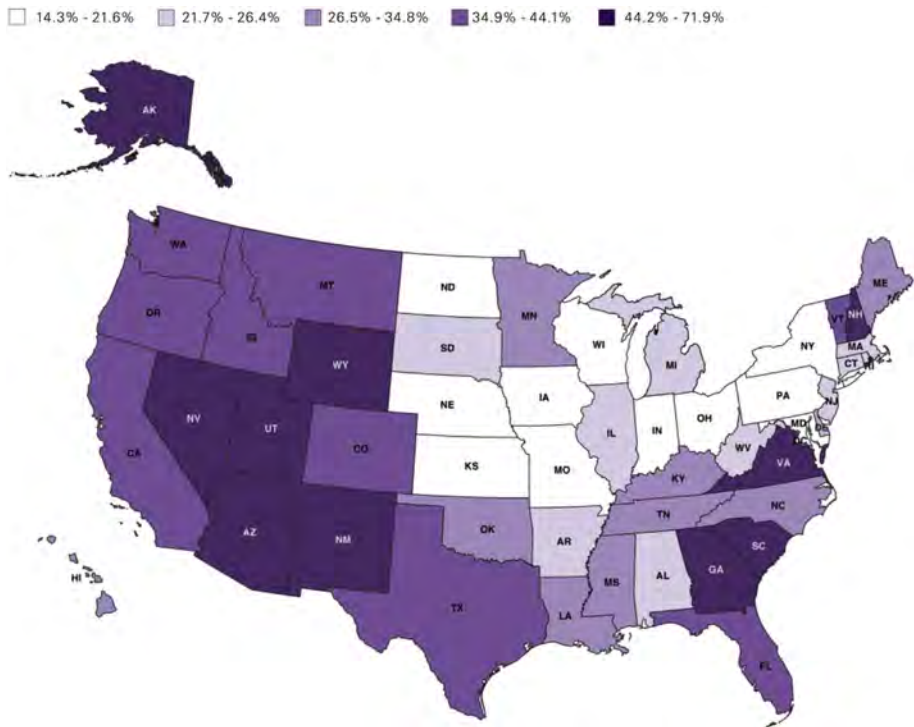


Fig. 2. Projected increases between 2015 and 2025 in Alzheimer's disease prevalence by state. Change from 2015 to 2025 for Washington, D.C.: -1.1%. Created from data provided to the Alzheimer's Association by Weuve and colleagues [154].^{A7}

outweighed by the aging of the population, and the social and economic burden of Alzheimer's and other dementias will continue to grow.

3.6. Looking to the future

The number of Americans surviving into their 80s, 90s and beyond is expected to grow dramatically due to advances in medicine and medical technology, as well as social and environmental conditions [167]. Additionally, a large segment of the American population—the baby boom generation—has begun to reach age 65 and older, when the risk for Alzheimer's and other dementias is elevated. By 2030, the

segment of the U.S. population age 65 and older will increase substantially, and the projected 72 million older Americans will make up approximately 20 percent of the total population (up from 13 percent in 2010) [167].

As the number of older Americans grows rapidly, so too will the numbers of new and existing cases of Alzheimer's disease, as shown in Fig. 4 [120].^{A11}

- In 2010, there were an estimated 454,000 new cases of Alzheimer's disease. By 2030, that number is projected to be 615,000 (a 35 percent increase), and by 2050, 959,000 (a 110 percent increase from 2010) [155].

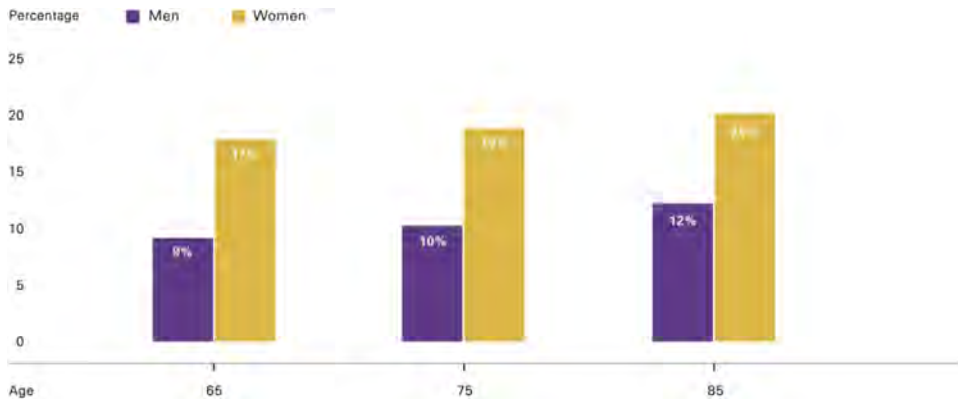


Fig. 3. Estimated lifetime risk for Alzheimer's, by age and sex, from the Framingham Study. Created from data from Seshadri and colleagues [156].

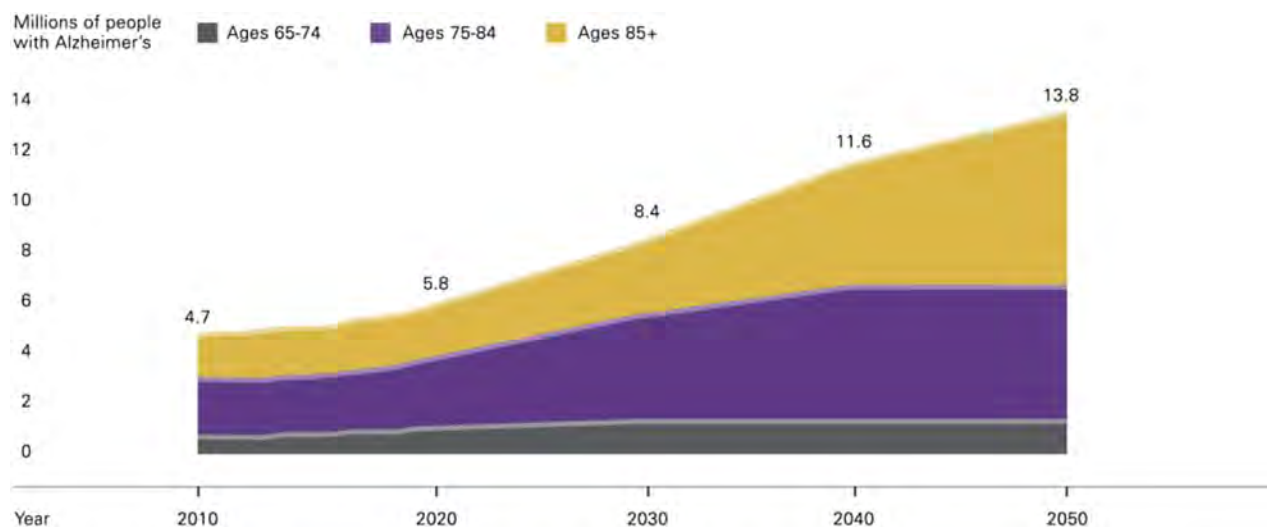


Fig. 4. Projected number of people age 65 and older (total and by age group) in the U.S. population with Alzheimer's disease, 2010 to 2050. Created from data from Hebert and colleagues [120].^{A11}

- By 2025, the number of people age 65 and older with Alzheimer's disease is estimated to reach 7.1 million—a 40 percent increase from the 5.1 million age 65 and older affected in 2015 [120].^{A12}
- By 2050, the number of people age 65 and older with Alzheimer's disease may nearly triple, from 5.1 million to a projected 13.8 million, barring the development of medical breakthroughs to prevent or cure the disease [120].^{A11} Previous estimates based on high range projections of population growth provided by the U.S. Census suggest that this number may be as high as 16 million [168].^{A13}

3.7. Growth of the oldest-old population

Longer life expectancies and aging baby boomers will also increase the number and percentage of Americans who will be among the oldest-old, individuals age 85 and older. Between 2010 and 2050, the oldest-old are expected to increase from 14 percent of all people age 65 and older in the United States to 20 percent of all people age 65 and older [167]. This will result in an additional 13 million oldest-old people—individuals at the highest risk for developing Alzheimer's [167].

- In 2015, about 2 million people who have Alzheimer's disease are age 85 or older, accounting for 38 percent of all people with Alzheimer's [120].
- When the first wave of baby boomers reaches age 85 (in 2031), it is projected that more than 3 million people age 85 and older will have Alzheimer's [120].
- By 2050, as many as 7 million people age 85 and older may have Alzheimer's disease, accounting for half (51 percent) of all people 65 and older with Alzheimer's [120].

4. Mortality and morbidity

Alzheimer's disease is officially listed as the sixth-leading cause of death in the United States [169]. It is the fifth-leading cause of death for those age 65 and older [169]. However, it may cause even more deaths than official sources recognize. Alzheimer's is also a leading cause of disability and poor health (morbidity). Before a person with Alzheimer's dies, he or she lives through years of morbidity as the disease progresses.

4.1. Deaths from Alzheimer's disease

It is difficult to determine how many deaths are caused by Alzheimer's disease each year because of the way causes of death are recorded. According to data from the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC), 84,767 people died from Alzheimer's disease in 2013 [169]. The CDC considers a person to have died from Alzheimer's if the death certificate lists Alzheimer's as the underlying cause of death, defined by the World Health Organization as "the disease or injury which initiated the train of events leading directly to death" [170]. However, death certificates for individuals with Alzheimer's often list acute conditions such as pneumonia as the primary cause of death rather than Alzheimer's [171–173]. Severe dementia frequently causes complications such as immobility, swallowing disorders and malnutrition that can significantly increase the risk of other serious conditions that can cause death. One such condition is pneumonia, which is the most commonly identified cause of death among elderly people with Alzheimer's disease and other dementias [174,175]. The number of people with Alzheimer's disease who die while experiencing these other conditions may not be counted among the number of people who died from Alzheimer's disease according to the CDC definition, even

though Alzheimer's disease is likely a contributing cause of death. Thus, it is likely that Alzheimer's disease is a contributing cause of death for more Americans than is indicated by CDC data. A recent study using data from the Rush Memory and Aging Project and the Religious Orders Study supports this concept; researchers estimated that 500,000 deaths among people age 75 and older could be attributed to Alzheimer's disease in the United States in 2010 (estimates for people age 65 to 74 were not available), meaning that those deaths would not be expected to occur in that year if those individuals did not have Alzheimer's [176].

The situation has been described as a "blurred distinction between death *with* dementia and death *from* dementia" [177]. According to data from the Chicago Health and Aging Project (CHAP), an estimated 600,000 people age 65 and older died *with* Alzheimer's in the United States in 2010, meaning they died after developing Alzheimer's disease [178]. Of these, an estimated 400,000 were age 85 and older, and an estimated 200,000 were age 65 to 84. Furthermore, according to Medicare data, one-third of all seniors who die in a given year have been diagnosed with Alzheimer's or another dementia [153,179]. Although some seniors who die with Alzheimer's disease die from causes that are unrelated to Alzheimer's, many of them die from Alzheimer's disease itself or from conditions in which Alzheimer's was a contributing cause, such as pneumonia. A recent study evaluating the contribution of individual common diseases to death using a nationally representative sample of older adults found that dementia was the second largest contributor to death behind heart failure [180]. Thus, for people who die with Alzheimer's, the disease is expected to be a significant direct contributor to their deaths.

In 2015, an estimated 700,000 people in the United States age 65 and older will die *with* Alzheimer's based on CHAP data [178]. The true number of deaths caused by Alzheimer's is likely to be somewhere between the official estimated numbers of those dying *from* Alzheimer's (as indicated by death certificates) and those dying *with* Alzheimer's. Regardless of the cause of death, among people age 70, 61 percent of those with Alzheimer's are expected to die before age 80 compared with 30 percent of people without Alzheimer's [181].

4.2. Public health impact of deaths from Alzheimer's disease

As the population of the United States ages, Alzheimer's is becoming a more common cause of death. Although deaths from other major causes have decreased significantly, official records indicate that deaths from Alzheimer's disease have increased significantly. Between 2000 and 2013, deaths attributed to Alzheimer's disease increased 71 percent, while those attributed to the number one cause of death (heart disease) decreased 14 percent (Fig. 5) [169]. The increase in the number and proportion of death certificates listing Alzheimer's as the underlying cause of death reflects both changes in patterns of reporting deaths on death certificates over time as well as an increase in the actual number of deaths attributable to Alzheimer's.

4.3. State-by-state deaths from Alzheimer's disease

Table 3 provides information on the number of deaths due to Alzheimer's by state in 2013, the most recent year for which state-by-state data are available. This information was obtained from death certificates and reflects the condition

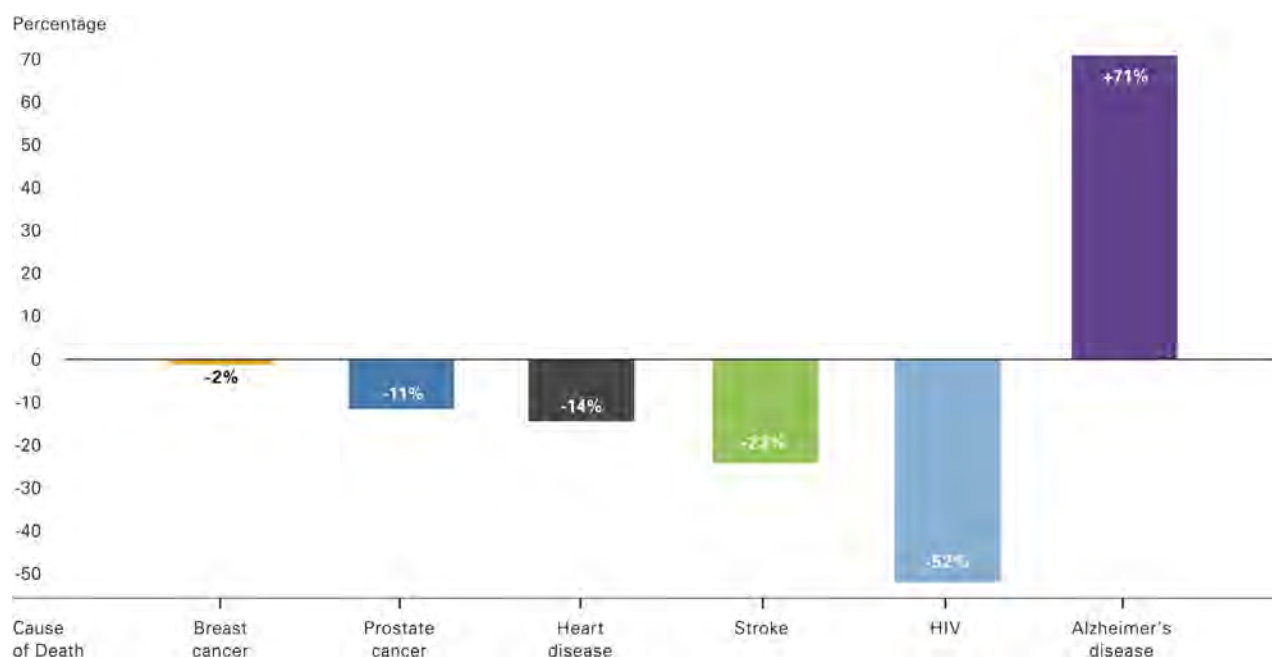


Fig. 5. Percentage changes in selected causes of death (all ages) between 2000 and 2013. Created from data from the National Center for Health Statistics [169].

Table 3
Number of deaths and annual mortality rate (per 100,000) due to Alzheimer's disease by state, 2013

State	Number of deaths	Mortality rate
Alabama	1398	28.9
Alaska	72	9.8
Arizona	2383	36.0
Arkansas	918	31.0
California	11,891	31.0
Colorado	1316	25.0
Connecticut	824	22.9
Delaware	192	20.7
District of Columbia	130	20.1
Florida	5093	26.0
Georgia	2048	20.5
Hawaii	260	18.5
Idaho	347	21.5
Illinois	2919	22.7
Indiana	2104	32.0
Iowa	1252	40.5
Kansas	742	25.6
Kentucky	1462	33.3
Louisiana	1505	32.5
Maine	401	30.2
Maryland	919	15.5
Massachusetts	1699	25.4
Michigan	3220	32.5
Minnesota	1427	26.3
Mississippi	925	30.9
Missouri	2026	33.5
Montana	267	26.3
Nebraska	557	29.8
Nevada	448	16.1
New Hampshire	351	26.5
New Jersey	1812	20.4
New Mexico	339	16.3
New York	2556	13.0
North Carolina	2872	29.2
North Dakota	363	50.2
Ohio	3798	32.8
Oklahoma	1145	29.7
Oregon	1312	33.4
Pennsylvania	3271	25.6
Rhode Island	346	32.9
South Carolina	1623	34.0
South Dakota	418	49.5
Tennessee	2536	39.0
Texas	5293	20.0
Utah	412	14.2
Vermont	269	42.9
Virginia	1642	19.9
Washington	3277	47.0
West Virginia	590	31.8
Wisconsin	1671	29.1
Wyoming	126	21.6
U.S. Total	84,767	26.8

NOTE. Created from data from the National Center for Health Statistics [169].^{A14}

identified by the physician as the underlying cause of death. The table also provides annual mortality rates by state to compare the risk of death due to Alzheimer's disease across states with varying population sizes and attributes. For the

United States as a whole, in 2013, the mortality rate for Alzheimer's disease was 27 deaths per 100,000 people [169].

4.4. Alzheimer's disease death rates

As shown in Fig. 6, the rate of deaths attributed to Alzheimer's has risen substantially since 2000 [169]. Table 4 shows that the rate of death from Alzheimer's increases dramatically with age, especially after age 65 [169]. The increase in the Alzheimer's death rate over time has disproportionately affected the oldest-old [182]. Between 2000 and 2013, the death rate from Alzheimer's did not increase for people age 65 to 74, but increased 23 percent for people age 75 to 84, and 39 percent for people age 85 and older.

4.5. Duration of illness from diagnosis to death

Studies indicate that people age 65 and older survive an average of 4 to 8 years after a diagnosis of Alzheimer's disease, yet some live as long as 20 years with Alzheimer's [183–188]. This reflects the slow, insidious progression of Alzheimer's. On average, a person with Alzheimer's disease will spend more years (40 percent of the total number of years with Alzheimer's) in the most severe stage of the disease than in any other stage [181]. Much of this time will be spent in a nursing home. Exemplifying this, nursing home admission by age 80 is expected for 75 percent of people with Alzheimer's compared with only 4 percent of the general population [181]. In all, an estimated two-thirds of those who die of dementia do so in nursing homes, compared with 20 percent of people with cancer and 28 percent of people dying from all other conditions [189].

4.6. Burden of Alzheimer's disease

The long duration of illness before death contributes significantly to the public health impact of Alzheimer's disease because much of that time is spent in a state of disability and dependence. Scientists have developed methods to measure and compare the burden of different diseases on a population in a way that takes into account both the number of years of life lost due to that disease as well as the number of healthy years of life lost by virtue of being in a state of disability. These measures indicate that Alzheimer's is a very burdensome disease and that the burden of Alzheimer's has increased more dramatically in the United States than other diseases in recent years. The primary measure of disease burden is called disability-adjusted life-years (DALYs), which is the sum of the number of years of life lost due to premature mortality and the number of years lived with disability. Using this measure, Alzheimer's rose from the 25th most burdensome disease in the United States in 1990 to the 12th in 2010. No other disease or condition increased as much [190]. In terms of years of life lost, Alzheimer's disease rose from 32nd to 9th, the largest increase for any disease. In terms of years lived with disability, Alzheimer's

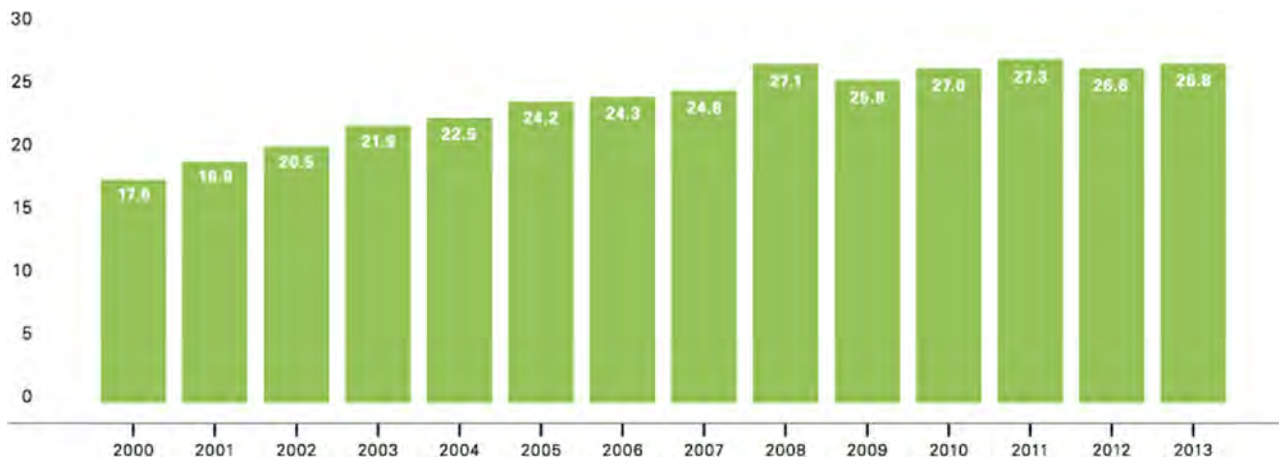


Fig. 6. U.S. annual Alzheimer's death rate (per 100,000) by year. Created from data from the National Center for Health Statistics [169].

disease went from ranking 17th to 12th; only kidney disease equaled Alzheimer's in as high a jump in rank.

Taken together, the numbers in this section indicate that not only is Alzheimer's disease responsible for the deaths of more and more Americans, the disease is also contributing to more and more cases of poor health and disability in the United States.

5. Caregiving

Caregiving refers to attending to another individual's health needs. Caregiving often includes assistance with one or more activities of daily living (ADLs) such as bathing and dressing [191,192]. More than 15 million Americans provide unpaid care for people with Alzheimer's disease and other dementias.^{A15}

5.1. Unpaid caregivers

Eighty-five percent of unpaid help provided to older adults in the United States is from family members [193]. Friends may provide unpaid caregiving as well. In 2014, caregivers of people with Alzheimer's disease and other dementias provided an estimated 17.9 billion hours of informal (that is, unpaid) assistance, a contribution to the nation valued at \$217.7 billion. This is approximately 46 percent of the net value of Walmart sales in 2013 (\$473.1 billion) [194] and nearly eight times the total revenue of McDonald's in 2013 (\$28.1 billion) [195]. According to a recent report [196], the

value of informal care (not including caregivers' out-of-pocket costs) was nearly equal to the costs of direct medical and long-term care of dementia.

The three primary reasons caregivers decide to provide care and assistance to a person with Alzheimer's disease are (1) the desire to keep a family member/friend at home (65 percent), (2) proximity to the person with dementia (48 percent) and (3) the caregiver's perceived obligation as a spouse or partner (38 percent).^{A16}

5.1.1. Who are the caregivers?

Several sources have examined the demographic background of family caregivers of people with Alzheimer's disease and other dementias in the United States [197–200].^{A16} Approximately two-thirds of caregivers are women [197,198],^{A16} and 34 percent are age 65 or older.^{A16} Over two-thirds of caregivers are married, living with a partner or in a long-term relationship [198].^{A16} More than two-thirds of caregivers are non-Hispanic white [198],^{A16} while 10 percent are African-American, 8 percent are Hispanic, and 5 percent are Asian.^{A16} Over 40 percent of dementia caregivers have a college degree or greater education [198].^{A16} Forty-one percent of caregivers have a household income of \$50,000 or less.^{A16} Over half of primary caregivers of people with dementia (individuals who indicate having the most responsibility for helping their relatives; 55 percent) take care of parents [200]. Most caregivers either live with the care recipient

Table 4

U.S. annual Alzheimer's death rate (per 100,000) by age

Age	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
45-54	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.2	0.2
55-64	2.0	2.1	1.9	2.0	1.8	2.1	2.1	2.2	2.2	2.0	2.1	2.2	2.2	2.2
65-74	18.7	18.6	19.6	20.7	19.5	20.2	19.9	20.2	21.1	19.4	19.8	19.2	17.9	18.1
75-84	139.6	147.2	157.7	164.1	168.5	177.0	175.0	175.8	192.5	179.1	184.5	183.9	175.4	171.6
85+	667.7	725.4	790.9	846.8	875.3	935.5	923.4	928.7	1002.2	945.3	987.1	967.1	936.1	929.5

NOTE. Created from data from the National Center for Health Statistics [169].

(27 percent) or live within 20 minutes of the care recipient (46 percent).^{A16} It is estimated that 250,000 children and young adults between ages 8 and 18 provide help to someone with Alzheimer's disease or another dementia [201].

5.1.2. Ethnic and racial diversity in caregiving

Among caregivers of people with Alzheimer's disease and other dementias, the National Alliance for Caregiving (NAC) and AARP found the following in 2009 [202]:

- Fifty-four percent of non-Hispanic white caregivers assist a parent, compared with 38 percent of individuals from other racial/ethnic groups.
- On average, Hispanic and African-American caregivers spend more time caregiving (approximately 30 hours per week) than non-Hispanic white caregivers (20 hours per week) and Asian-American caregivers (16 hours per week).
- Hispanic (45 percent) and African-American (57 percent) caregivers are more likely to experience high burden from caregiving than non-Hispanic white caregivers (33 percent) and Asian-American caregivers (30 percent).

5.1.3. Sandwich generation caregivers

Traditionally, the term “sandwich generation caregiver” has referred to a middle-aged person who simultaneously cares for dependent minor children and aging parents. The phenomenon of sandwich generation caregiving has received a good deal of attention in recent years as it has been argued that demographic changes (such as parents of dependent minors being older than in the past along with the aging of the U.S. population) have led to increases in the number of sandwich generation caregivers [203–205]. National surveys have found that 23 percent of Alzheimer's disease and dementia caregivers lived with children under the age of 18.^{A16} Other studies have found that sandwich generation caregivers are present in 8 to 13 percent of households in the United States [206,207]. It is not clear what proportion of care recipients in

these studies had Alzheimer's disease or another dementia, but in other studies of sandwich generation caregivers about one-third of elderly care recipients have Alzheimer's disease or another dementia [197]. Sandwich generation caregivers indicate lower quality of life and diminished health behaviors (for example, less likely to choose foods based on health values; less likely to use seat belts; less likely to exercise) compared with non-sandwich generation caregivers or non-caregivers [208,209].

5.1.4. Caregiving tasks

The care provided to people with Alzheimer's disease and other dementias is wide-ranging and in some instances all-encompassing. Table 5 summarizes some of the most common types of dementia care provided.

Though the care provided by family members of people with Alzheimer's disease and other dementias is somewhat similar to the help provided by caregivers of people with other conditions, dementia caregivers tend to provide more extensive assistance. Family caregivers of people with dementia are more likely than caregivers of other older people to assist with any ADL (Fig. 7). More than half of dementia caregivers report providing help with getting in and out of bed, and about one-third provide help with getting to and from the toilet, bathing, managing incontinence and feeding. These findings are consistent with the heightened degree of dependency experienced by many people with Alzheimer's disease and other dementias. Fewer caregivers of other older people report providing help with each of these types of care [202]. Data from the 2011 National Survey of Caregiving (NSOC) indicated that caregivers of people with dementia [210] are more likely than caregivers of people without dementia to provide help with self-care and mobility (85 percent versus 71 percent) and health or medical care (63 percent versus 52 percent) [197,211]. Individuals with dementia are also more likely than those without dementia to rely on multiple unpaid caregivers; 39 percent of people with dementia rely on three or more unpaid caregivers,

Table 5

Dementia caregiving tasks

Help with instrumental activities of daily living (IADLs), such as household chores, shopping, preparing meals, providing transportation, arranging for doctor's appointments, managing finances and legal affairs and answering the telephone.
Helping the person take medications correctly, either via reminders or direct administration of medications.
Helping the person adhere to treatment recommendations for dementia or other medical conditions.
Assisting with personal activities of daily living (ADLs), such as bathing, dressing, grooming, feeding and helping the person walk, transfer from bed to chair, use the toilet and manage incontinence.
Managing behavioral symptoms of the disease such as aggressive behavior, wandering, depressive mood, agitation, anxiety, repetitive activity and nighttime disturbances.
Finding and using support services such as support groups and adult day service programs.
Making arrangements for paid in-home, nursing home or assisted living care.
Hiring and supervising others who provide care.
Assuming additional responsibilities that are not necessarily specific tasks, such as:
<ul style="list-style-type: none"> • Providing overall management of getting through the day. • Addressing family issues related to caring for a relative with Alzheimer's disease, including communication with other family members about care plans, decision-making and arrangements for respite for the main caregiver.

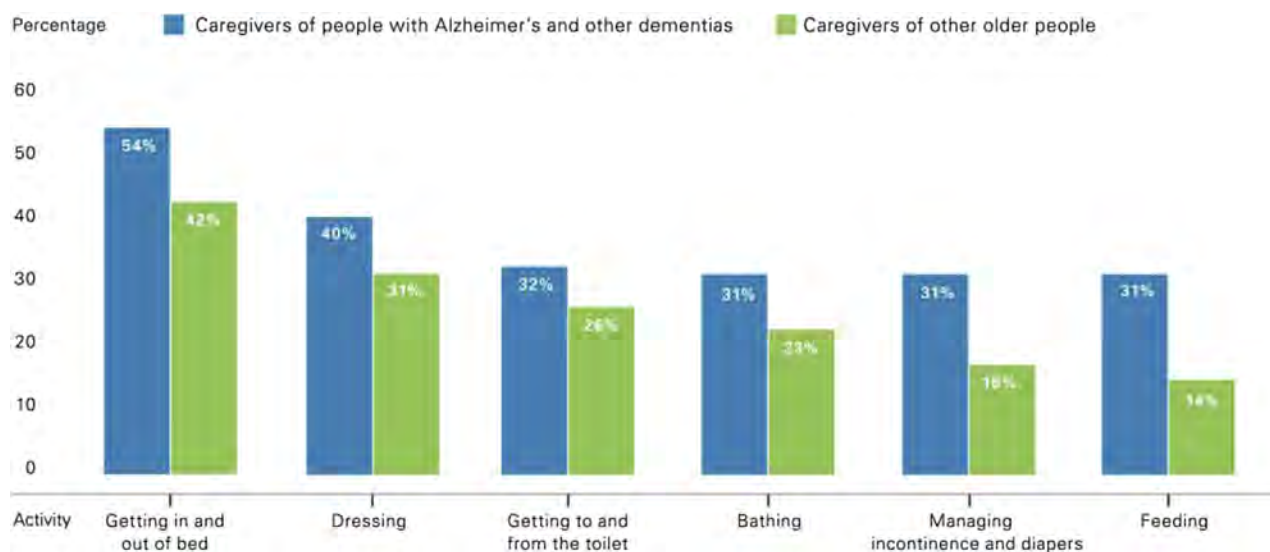


Fig. 7. Proportion of caregivers of people with Alzheimer's and other dementias vs caregivers of other older people who provide help with specific activities of daily living, United States, 2009. Created from data from the National Alliance for Caregiving and AARP [202].

whereas 30 percent of people without dementia rely on three or more unpaid individuals [197].

In addition to assisting with ADLs, almost two-thirds of caregivers of people with Alzheimer's and other dementias advocate for their care recipient with government agencies and service providers (64 percent), and nearly half arrange and supervise paid caregivers from community agencies (46 percent). By contrast, caregivers of other older adults are less likely to advocate for their family member (50 percent) and supervise community-based care (33 percent) [202]. Caregivers of people with dementia are more likely to coordinate health care for the care recipient compared with caregivers of people without dementia (86 percent versus 72 percent) [197]. Caring for a person with dementia also means managing symptoms that family caregivers of people with other diseases may not face, such as neuropsychiatric symptoms and severe behavioral problems. Family caregivers often lack the information or resources necessary to manage the increasing complexity of medication regimens for people with dementia [212].

When a person with Alzheimer's or another dementia moves to an assisted living residence or nursing home, the help provided by his or her family caregiver usually changes from the comprehensive care summarized in Table 5 to providing emotional support, interacting with facility staff, and advocating for appropriate care. However, some family caregivers continue to help with bathing, dressing and other ADLs [213–215]. Admitting a relative to a residential care facility has mixed effects on the emotional and psychological well-being of family caregivers. Some studies suggest that distress remains unchanged or even increases after a relative is admitted to a residential care facility, but other studies have found that distress declines significantly after admission [215–217]. The relationship between the care-

giver and person with dementia may explain these discrepancies. For example, husbands, wives and daughters are significantly more likely than other family caregivers to indicate persistent burden up to 12 months following placement, while husbands are more likely than other family caregivers to indicate persistent depression up to a year following a relative's admission to a residential care facility [216].

5.1.5. Duration of caregiving

Eighty-six percent of dementia caregivers have provided care and assistance for at least the past year, according to the 2014 Alzheimer's Association Women and Alzheimer's Poll.^{A16} Caregivers of people with Alzheimer's and other dementias provide care for a longer time, on average, than caregivers of older adults with other conditions. As shown in Fig. 8, 43 percent of caregivers of people with Alzheimer's and other dementias provided care for 1 to 4 years compared with 33 percent of caregivers of people without dementia. Similarly, 32 percent of dementia caregivers provide care for 5 years or more compared with 28 percent of caregivers of people without dementia [202].

5.1.6. Hours of unpaid care and economic value of caregiving

In 2014, the 15.7 million family and other unpaid caregivers of people with Alzheimer's disease and other dementias provided an estimated 17.9 billion hours of unpaid care. This number represents an average of 21.9 hours of care per caregiver per week, or 1139 hours of care per caregiver per year.^{A17} With this care valued at \$12.17 per hour,^{A18} the estimated economic value of care provided by family and other unpaid caregivers of people with dementia was \$217.7 billion in 2014. Table 6 shows the total hours of unpaid care as well as the value of care provided by family and other

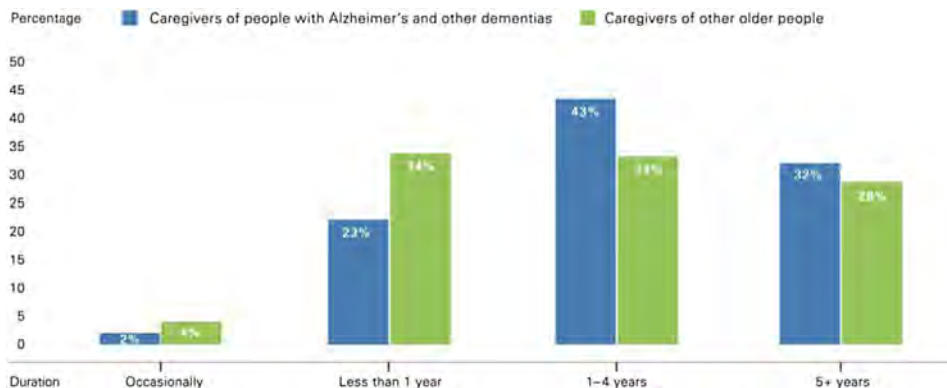


Fig. 8. Proportion of Alzheimer's and dementia caregivers vs caregivers of other older people by duration of caregiving, United States, 2009. Created from data from the National Alliance for Caregiving and AARP [202].

unpaid caregivers for the United States and each state. Unpaid caregivers of people with Alzheimer's and other dementias provided care valued at more than \$1 billion in each of 39 states. Unpaid caregivers in each of the four most populous states—California, Florida, New York and Texas—provided care valued at more than \$14 billion. Additional research is needed to estimate the future value of family care for people with Alzheimer's disease as the U.S. population continues to age.

Caregivers of people with dementia report providing 27 hours' more care per month on average (92 hours versus 65 hours) than caregivers of people without dementia [197]. Other studies suggest that primary family caregivers provide particularly extensive amounts of care to people who have dementia. For example, a 2011 report found that primary family caregivers of people with dementia reported spending an average of 9 hours per day providing help to their relatives [200]. In addition, many caregivers of people with Alzheimer's disease or another dementia provide help alone. Forty-one percent of dementia caregivers in the 2014 Alzheimer's Association poll reported that no one else provided unpaid assistance.^{A16}

5.1.7. Impact of Alzheimer's disease caregiving

Caring for a person with Alzheimer's or another dementia poses special challenges. For example, people with Alzheimer's disease experience losses in judgment, orientation and the ability to understand and communicate effectively. Family caregivers must often help people with Alzheimer's manage these issues. The personality and behavior of a person with Alzheimer's are affected as well, and these changes are often among the most challenging for family caregivers [218]. Individuals with Alzheimer's also require increasing levels of supervision and personal care as the disease progresses. As symptoms worsen with the progression of a relative's dementia, the care required of family members can result in increased emotional stress and depression; new or exacerbated health problems; and depleted income and finances due in part to disruptions in employment

[219–224].^{A16} The intimacy and history of experiences and memories that are often part of the relationship between a caregiver and care recipient may also be threatened due to the memory loss, functional impairment and psychiatric/behavioral disturbances that can accompany the progression of Alzheimer's disease.

5.1.7.1. Caregiver emotional well-being

Although caregivers report some positive feelings about caregiving such as family togetherness and the satisfaction of helping others [225],^{A16} they also report high levels of stress when providing care:

- Based on a Level of Care Index that combined the number of hours of care and the number of ADLs tasks performed by the caregiver, fewer dementia caregivers in the 2009 NAC/AARP survey were classified in the lowest level of burden than caregivers of people without dementia (16 percent versus 31 percent, respectively) [202].
- Approximately 18 percent of caregivers of people with dementia, in contrast to only 6 percent of caregivers of people without dementia, indicate substantial negative aspects of caregiving [197].
- Compared with caregivers of people without dementia, twice as many caregivers of people with dementia indicate substantial financial, emotional and physical difficulties [197].
- Fifty-nine percent of family caregivers of people with Alzheimer's and other dementias rated the emotional stress of caregiving as high or very high (Fig. 9).^{A16}
- Many family caregivers report “a good amount” to “a great deal” of caregiving strain concerning financial issues (47 percent).^{A16}
- Approximately 40 percent of family caregivers of people with dementia suffer from depression, compared with 5 to 17 percent of non-caregivers of similar ages [223,226–229]. Rates of depression increase with the severity of cognitive impairment of the person with dementia [230,231].

Table 6

Number of Alzheimer's disease and dementia (AD/D) caregivers, hours of unpaid care, economic value of unpaid care and higher health care costs of caregivers by state, 2014*

State	AD/D caregivers (in thousands)	Hours of unpaid care (in millions)	Value of unpaid care (in millions of dollars)	Higher health care costs of caregivers (in millions of dollars) [†]
Alabama	301	342	\$4166	\$171
Alaska	33	38	\$458	\$27
Arizona	314	357	\$4345	\$155
Arkansas	174	198	\$2410	\$97
California	1573	1791	\$21,795	\$895
Colorado	234	266	\$3243	\$128
Connecticut	177	201	\$2450	\$139
Delaware	52	60	\$725	\$40
District of Columbia	27	31	\$378	\$26
Florida	1058	1205	\$14,669	\$688
Georgia	506	576	\$7015	\$251
Hawaii	65	74	\$901	\$41
Idaho	78	89	\$1084	\$40
Illinois	589	671	\$8163	\$362
Indiana	332	379	\$4608	\$201
Iowa	134	152	\$1853	\$84
Kansas	150	171	\$2075	\$92
Kentucky	269	306	\$3725	\$161
Louisiana	230	262	\$3186	\$142
Maine	68	78	\$946	\$53
Maryland	289	329	\$4001	\$197
Massachusetts	329	374	\$4554	\$277
Michigan	508	578	\$7035	\$305
Minnesota	248	282	\$3430	\$167
Mississippi	205	234	\$2846	\$122
Missouri	312	355	\$4326	\$198
Montana	48	55	\$668	\$29
Nebraska	81	92	\$1117	\$52
Nevada	140	159	\$1937	\$73
New Hampshire	65	74	\$905	\$47
New Jersey	447	509	\$6189	\$308
New Mexico	106	121	\$1467	\$64
New York	1017	1158	\$14,091	\$771
North Carolina	448	510	\$6208	\$263
North Dakota	30	34	\$414	\$21
Ohio	594	676	\$8229	\$382
Oklahoma	220	250	\$3046	\$130
Oregon	175	199	\$2422	\$105
Pennsylvania	671	765	\$9304	\$472
Rhode Island	53	60	\$731	\$40
South Carolina	295	336	\$4092	\$169
South Dakota	37	42	\$514	\$24
Tennessee	422	480	\$5847	\$245
Texas	1331	1516	\$18,446	\$716
Utah	142	162	\$1969	\$65
Vermont	30	34	\$413	\$21
Virginia	452	514	\$6259	\$258
Washington	324	369	\$4485	\$200
West Virginia	108	123	\$1499	\$75
Wisconsin	191	218	\$2650	\$127
Wyoming	28	32	\$384	\$18
U.S. Totals	15,706	17,886	\$217,670	\$9733

NOTE. Created from data from the 2009 BRFSS, U.S. Census Bureau, Centers for Medicare and Medicaid Services, National Alliance for Caregiving, AARP and U.S. Department of Labor.^{A13, A15, A16, A17}

*State totals may not add up to the U.S. total due to rounding.

[†]Higher health care costs are the dollar amount difference between the weighted per capita personal health care spending of caregivers and non-caregivers in each state.^{A19}

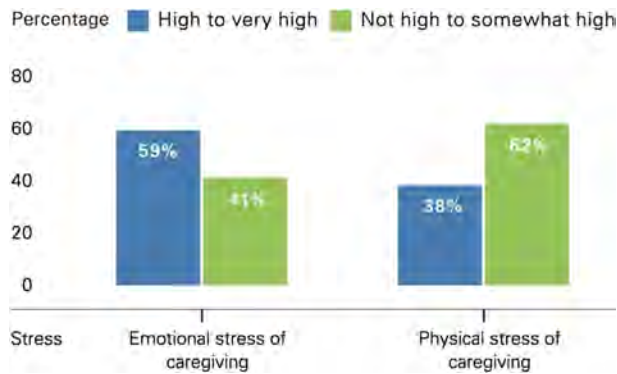


Fig. 9. Proportion of Alzheimer's and dementia caregivers who report high or very high emotional and physical stress due to caregiving. Created from data from the Alzheimer's Association.^{A16}

- In the 2009 NAC/AARP survey, caregivers most likely to indicate stress were women, older, residing with the care recipient, and white or Hispanic [202].
- According to the 2014 Alzheimer's Association poll, respondents often believed they had no choice in taking on the role of caregiver.^{A16}
- The 2014 Alzheimer's Association poll found that women with children under age 18 felt that caregiving for someone with Alzheimer's disease was more challenging than caring for children (53 percent).^{A16}
- When caregivers report being stressed because of the impaired person's behavioral symptoms, it increases the chance that they will place the care recipient in a nursing home [202,232].
- Seventy-three percent of family caregivers of people with Alzheimer's disease and other dementias agree that it is neither "right nor wrong" when families decide to place their family member in a nursing home. Yet many such caregivers experience feelings of guilt, emotional upheaval and difficulties in adapting to the admission transition (for example, interacting with care staff to determine an appropriate care role for the family member) [213,215,233,234].^{A16}
- The demands of caregiving may intensify as people with dementia approach the end of life [235]. In the year before the person's death, 59 percent of caregivers felt they were "on duty" 24 hours a day, and many felt that caregiving during this time was extremely stressful [236]. One study of end-of-life care found that 72 percent of family caregivers experienced relief when the person with Alzheimer's disease or another dementia died [236].

5.1.7.2. Caregiver physical health

For some caregivers, the demands of caregiving may cause declines in their own health. Evidence suggests that the stress of dementia care provision increases caregivers' susceptibility to disease and health complications [237].

As shown in Fig. 9, 38 percent of Alzheimer's and dementia caregivers indicate that the physical impact of caregiving was high to very high.^{A16} Sleep disturbances, which can occur frequently when caring for a relative with Alzheimer's disease or another dementia, have also been shown to negatively influence family caregivers' health [238,239].

5.1.7.2.1. General health

Seventy-four percent of caregivers of people with Alzheimer's disease and other dementias reported that they were "somewhat concerned" to "very concerned" about maintaining their own health since becoming a caregiver.^{A16} Dementia caregivers were more likely than non-caregivers to report that their health was fair or poor [221]. Dementia caregivers were also more likely than caregivers of other older people to say that caregiving made their health worse [202,240]. The 2009 and 2010 Behavioral Risk Factor Surveillance System (BRFSS) surveys found that 7 percent of dementia caregivers say the greatest difficulty of caregiving is that it creates or aggravates their own health problems compared with 2 percent of other caregivers [198]. According to 1998–2010 bi-annual data from the Health and Retirement Survey, dementia caregivers were much more likely (41 percent increased odds) to become more frail from the period prior to the death of a spouse receiving care to the spouse's death [241]. Other studies suggest that caregiving tasks have the positive effect of keeping older caregivers more physically active than non-caregivers [242].

5.1.7.2.2. Physiological changes

The chronic stress of caregiving is associated with physiological changes that could increase the risk of developing chronic conditions. For example, a series of recent studies found that under certain circumstances some Alzheimer's caregivers were more likely to have elevated biomarkers of cardiovascular disease risk and impaired kidney function risk than those who were not caregivers [243–248].

Caregivers of a spouse with Alzheimer's or another dementia are more likely than married non-caregivers to have physiological changes that may reflect declining physical health, including high levels of stress hormones [249], reduced immune function [219,250], slow wound healing [251], and increased incidence of hypertension [252], coronary heart disease [253] and impaired endothelial function (the endothelium is the inner lining of the blood vessels). Some of these changes may be associated with an increased risk of cardiovascular disease [254]. Overall, the literature is fairly consistent in suggesting that the chronic stress of dementia care can have potentially negative influences on caregiver health.

5.1.7.2.3. Health care

The physical and emotional impact of dementia caregiving is estimated to have resulted in \$9.7 billion in health care costs in the United States in 2014.^{A19} Table 6 shows

the estimated higher health care costs for Alzheimer's and dementia caregivers in each state. In separate studies, hospitalization and emergency department visits were more likely for dementia caregivers who helped care recipients who were depressed, had low functional status or had behavioral disturbances [255].

5.1.7.2.4. Mortality

The health of a person with dementia may also affect the caregiver's risk of dying, although studies have reported mixed findings on this issue. In one study, caregivers of spouses who were hospitalized and had dementia in their medical records were more likely to die in the following year than caregivers whose spouses were hospitalized but did not have dementia, even after accounting for the age of caregivers [256]. However, other studies have found that caregivers in general have lower mortality rates than non-caregivers [257,258]. One study reported that higher levels of stress were associated with higher rates of mortality in both caregivers in general and non-caregivers [258]. These findings suggest that it is high stress, not caregiving per se, that increases the risk of mortality. Such results emphasize that dementia caregiving is a complex undertaking; simply providing care to someone with Alzheimer's disease or another dementia may not consistently result in stress or negative health problems for caregivers. Instead, the stress of dementia caregiving is influenced by a number of other factors, such as dementia severity, how challenging caregivers perceive certain aspects of care to be, available social support and caregiver personality. All of these factors are important to consider when understanding the health impact of caring for a person with dementia [259].

5.1.7.3. Caregiver employment

Among caregivers of people with Alzheimer's disease and other dementias, 75 percent reported being employed at any time since assuming care responsibilities.

Eighty-one percent of Alzheimer's caregivers under age 65 had been or were employed, while 35 percent age 65 and older had been or were employed [202]. Seventeen percent of dementia caregivers had to give up their jobs before or after assuming caregiving responsibilities. Among those who were employed at any time since they became caregivers, 9 percent ultimately quit their jobs to continue providing care. Fifty-four percent had to go in late or leave early, and 15 percent had to take a leave of absence. Other work-related challenges for dementia caregivers who had been employed at any time since beginning caregiving are summarized in Fig. 10.^{A16}

5.1.8. Interventions designed to assist caregivers

Strategies to support family caregivers of people with Alzheimer's disease have been developed and evaluated. The types and focus of these strategies (often called "interventions") are summarized in Table 7 [260,261].

In general, interventions aim to improve the health and well-being of dementia caregivers by relieving the negative aspects of caregiving. Some also aim to delay nursing home admission of the person with dementia. Specific approaches used in various interventions include helping caregivers manage dementia-related symptoms, improving social support for caregivers, and providing caregivers with respite from caregiving duties.

Three characteristics distinguish interventions that have been found to be particularly effective: they (1) assist caregivers over long periods; (2) approach dementia care as an issue for the entire family; and (3) train dementia caregivers in the management of behavioral problems [262–265]. Multicomponent approaches that combine individual and family counseling, education and other support over time appear especially beneficial in helping caregivers manage changes that occur as the care recipient's dementia progresses [266,267]. Examples of successful multicomponent

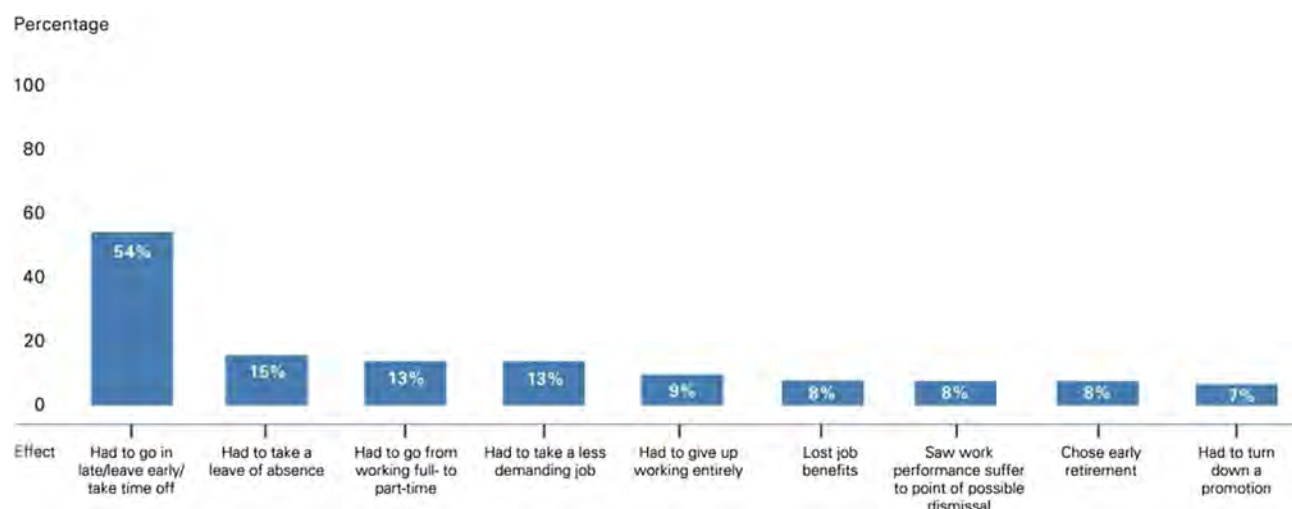


Fig. 10. Work-related changes among caregivers of people with Alzheimer's disease and other dementias who had been employed at any time since they began caregiving. Created from data from the Alzheimer's Association.^{A16}

Table 7
Type and focus of caregiver interventions

Type of intervention	Description
Case management	Provides assessment, information, planning, referral, care coordination and/or advocacy for family caregivers.
Psychoeducational	Includes a structured program that provides information about the disease, resources and services, and about how to expand skills to effectively respond to symptoms of the disease (that is, cognitive impairment, behavioral symptoms and care-related needs). Includes lectures, discussions and written materials and is led by professionals with specialized training.
Counseling	Aims to resolve pre-existing personal problems that complicate caregiving to reduce conflicts between caregivers and care recipients and/or improve family functioning.
Support groups	Less structured than psychoeducational or therapeutic interventions, support groups provide caregivers the opportunity to share personal feelings and concerns to overcome feelings of social isolation.
Respite	Provides planned, temporary relief for the caregiver through the provision of substitute care; examples include adult day services and in-home or institutional respite for a certain number of weekly hours.
Training of the person with dementia	Includes memory clinic or similar programs aimed at improving the competence of the care recipient, which may also have a positive effect on caregiver outcomes.
Psychotherapeutic approaches	Involve the establishment of a therapeutic relationship between the caregiver and a professional therapist (for example, cognitive-behavioral therapy for caregivers to focus on identifying and modifying beliefs related to emotional distress, developing new behaviors to deal with caregiving demands, and fostering activities that can promote caregiver well-being).
Multicomponent approaches	Are characterized by intensive support strategies that combine multiple forms of interventions, such as education, support and respite into a single, long-term service (often provided for 12 months or more).

NOTE. Created from data from Sørensen and colleagues and Pinquart and colleagues. [260,261].

interventions are the New York University Caregiver Intervention [268–270], the Resources for Enhancing Alzheimer's Caregiver Health (REACH) II protocol [271], the Savvy Caregiver program [272–274], the Reducing Disability in Alzheimer's Disease intervention [275] and the Skills2Care Program [276]. Other multicomponent approaches that have recently shown promise include: (1) Partners in Dementia Care, a care coordination program that improves access to needed services and strengthens the family support network [277] and (2) Acquiring New Skills While Enhancing Remaining Strengths (ANSWERS) [278], a program that combines training for the caregiver and person with dementia to help manage symptoms such as memory loss. Other current, promising intervention strategies include care coordination and approaches in which people with early-stage Alzheimer's disease and their family caregivers are educated together [279–290].

Interventions for dementia caregivers that have demonstrated efficacy in randomized controlled evaluations have been gradually implemented in the community [291–298]. These implementation efforts are generally successful at improving how caregiver services are delivered, reaching a larger number of families and helping caregivers cope with their responsibilities. Because caregivers and the settings in which they provide care are diverse, more studies are needed to define which interventions are most effective for specific situations [299]. Improved tools to “personalize” services for caregivers to maximize their benefits is an emerging area of research [265,300]. More studies are also needed to explore the effectiveness of interventions in different racial, ethnic, socioeconomic and geographic settings [301–305].

Growing evidence supports the effectiveness of respite services for caregivers [306]. Recent studies of adult day

service programs suggest that use of these services can improve dementia caregivers' emotional well-being and can have beneficial effects on biological indicators of stress and health for caregivers [307,308]. Although less consistent in their demonstrated benefits, in-person and online support groups (such as alzconnected.org) have the potential to offer encouragement and enhance caregiver outcomes.

5.1.9. Caregiver interventions and their effects on care recipients

Several reviews have sought to determine whether caregiver interventions improve outcomes for care recipients who have Alzheimer's disease or other dementias. One recent review found that caregiver-focused interventions are effective at reducing behavioral or psychiatric problems in care recipients who have dementia [309]. Multicomponent interventions for dementia caregivers have also been shown to prevent or delay nursing home admission of the care recipient [310–312]. However, these conclusions are not uniform; a recent review that restricted its scope to randomized controlled evaluations found that caregiver interventions had no consistent effects on outcomes of care recipients who had Alzheimer's disease or other dementias [313].

5.2. Paid caregivers

5.2.1. Direct-care workers for people with Alzheimer's disease and other dementias

Direct-care workers, such as nurse aides, home health aides and personal and home care aides, provide most of the long-term care services and supports for older adults (including those with Alzheimer's disease and other

dementias). In nursing homes, nursing assistants make up the majority of staff who work with cognitively impaired residents [314–316]. Nursing assistants help with bathing, dressing, housekeeping, food preparation and other activities. Most nursing assistants are women, and they come from increasingly diverse ethnic, racial and international backgrounds.

Direct-care workers have difficult jobs, and they may not receive the training necessary to provide dementia care [315,317]. One review found that direct-care workers received, on average, 75 hours of training and that this training included little focus on issues specific or pertinent to dementia care [315]. Turnover rates are high among direct-care workers, and recruitment and retention are persistent challenges [318]. Reviews have shown that staff training programs to improve the quality of dementia care in nursing homes have modest, positive benefits [317].

5.2.2. Shortage of geriatric health care professionals in the United States

Professionals who may receive special training in caring for older adults include physicians, nurse practitioners, registered nurses, social workers, pharmacists, physician assistants, case workers and others [318]. It is projected that the United States will need an additional 3.5 million health care professionals by 2030 just to maintain the current ratio of health care professionals to the older population [318]. The need for health care professionals trained in geriatrics is escalating, but few providers choose this career path. It is estimated that the United States has approximately half the number of certified geriatricians that it currently needs [319]. In 2010, there were 4278 physicians practicing geriatric medicine in the United States [320]. An estimated 36,000 geriatricians will be required to adequately meet the needs of older adults in the United States by 2030 [318]. Other health-related professions also have low numbers of geriatric specialists relative to the population's needs. According to the Institute of Medicine, less than 1 percent of registered nurses, physician assistants and pharmacists identify themselves as specializing in geriatrics [318]. Similarly, although 73 percent of social workers serve clients age 55 and older and about 8 percent are employed in long-term care settings, only 4 percent have formal certification in geriatric social work [318].

Because the complex care challenges of many people with dementia often require the simultaneous expertise of professionals trained in multiple care disciplines, there is a continuing need for interprofessional collaboration and education to enhance the overall care of people with dementia [321–323]. Ongoing efforts have attempted to integrate innovative care management practices alongside traditional primary care for people with dementia. Dementia care management often involves a skilled professional who serves as the care “manager” of the person with dementia. The care manager collaborates with primary care physicians or nurse practitioners to develop personalized care plans. These plans

can provide support to family caregivers, help people with dementia manage care transitions (for example, a change in care provider or site of care), and ensure the person with dementia's access to appropriate community-based services. Several evaluations have suggested that such approaches have considerable potential for improving outcomes for people with dementia and their family caregivers [324–328]. Current research is attempting to determine the feasibility of these models beyond the specialty settings in which they currently operate [329].

6. Use and costs of health care, long-term care and hospice

The costs of health care, long-term care and hospice for individuals with Alzheimer's disease and other dementias are substantial, and Alzheimer's disease is one of the costliest chronic diseases to society [196]. Total payments in 2015 (in 2015 dollars) for all individuals with Alzheimer's disease and other dementias are estimated at \$226 billion (Fig. 11). Medicare and Medicaid are expected to cover \$153 billion, or 68 percent, of the total health care and long-term care payments for people with Alzheimer's disease and other dementias. Out-of-pocket spending is expected to be \$44 billion, or 19 percent of total payments.^{A20}

6.1. Total cost of health care, long-term care and hospice

Table 8 reports the average annual per-person payments for health care and long-term care services for Medicare beneficiaries age 65 and older with and without Alzheimer's disease and other dementias. Unless otherwise indicated, all costs in this section are reported in 2014 dollars.^{A21} Total per-person health care and long-term care payments in 2014 from all sources for Medicare beneficiaries with Alzheimer's and other dementias were three times as great as payments for other Medicare beneficiaries in the same age

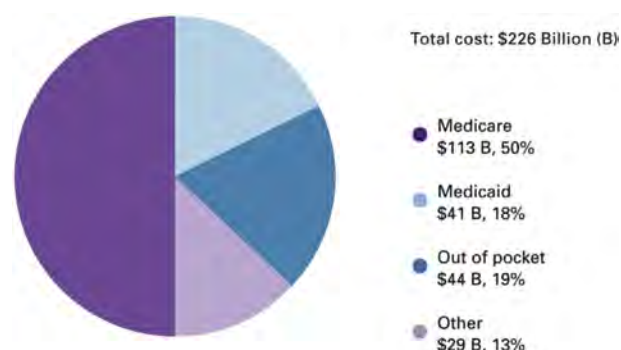


Fig. 11. Aggregate cost of care by payment source for Americans age 65 and older with Alzheimer's disease and other dementias, 2015. Data are in 2015 dollars. “Other” payment sources include private insurance, health maintenance organizations, other managed care organizations, and uncompensated care. Totals for payment sources may not add to total cost due to rounding. Created from the Lewin Model.^{A20}

Table 8

Average annual per-person payments for health care and long-term care services, Medicare beneficiaries age 65 and older, with and without Alzheimer's disease and other dementias and by place of residence, in 2014 dollars

Payment source	Beneficiaries with Alzheimer's disease and other dementias by place of residence			Beneficiaries without Alzheimer's disease and other dementias
	Overall	Community-dwelling	Residential facility	
Medicare	\$21,585	\$19,223	\$24,884	\$8191
Medicaid	11,021	242	26,086	574
Uncompensated	297	427	117	335
HMO	1083	1681	247	1579
Private insurance	2463	2707	2122	1657
Other payer	986	178	2115	156
Out of pocket	10,202	3449	19,642	2487
Total*	\$47,752	28,102	75,217	15,115

NOTE. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008 [179].

*Payments from sources do not equal total payments exactly due to the effect of population weighting. Payments for all beneficiaries with Alzheimer's disease and other dementias include payments for community-dwelling and facility-dwelling beneficiaries.

group (\$47,752 per person for those with dementia compared with \$15,115 per person for those without dementia) [179].^{A22}

Twenty-nine percent of older individuals with Alzheimer's disease and other dementias who have Medicare also have Medicaid coverage, compared with 11 percent of individuals without dementia [179]. Medicaid pays for nursing home and other long-term care services for some people with very low income and low assets, and the high use of these services by people with dementia translates into high costs for the Medicaid program. Average Medicaid payments per person for Medicare beneficiaries with Alzheimer's disease and other dementias (\$11,021) were 19 times as great as average Medicaid payments for Medicare beneficiaries without Alzheimer's disease and other dementias (\$574) (Table 8) [179].

Despite these and other sources of financial assistance, individuals with Alzheimer's disease and other dementias still incur high out-of-pocket costs. These costs are for Medicare and other health insurance premiums and for deductibles, copayments and services not covered by Medicare, Medicaid or additional sources of support. Medicare beneficiaries age 65 and older with Alzheimer's and other dementias paid \$10,202 out of pocket, on average, for health care and long-term care services not covered by other sources (Table 8) [179]. Average per-person out-of-pocket payments were highest (\$19,642 per person) for individuals living in nursing homes and assisted living facilities and were almost six times as great as the average per-person payments for individuals with Alzheimer's disease and other dementias living in the community [179].

Recently, researchers evaluated the additional or "incremental" health care and caregiving costs of dementia (that is, the costs specifically attributed to dementia when comparing people with and without dementia who have the same coexisting medical conditions and demographic characteristics) [196,330]. One group of researchers found that the incremental health care and nursing home costs

for those with dementia was \$28,501 per year in 2010 dollars (\$31,864 in 2014 dollars) [196].^{A21,A23}

6.2. Use and costs of health care services

People with Alzheimer's disease and other dementias have more than three times as many hospital stays per year as other older people [179]. Moreover, the use of health care services for people with other serious medical conditions is strongly affected by the presence or absence of dementia. In particular, people with coronary artery disease, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD), stroke or cancer who *also* have Alzheimer's and other dementias have higher use and costs of health care services than people with these medical conditions but no coexisting dementia.

6.2.1. Use of health care services

Older people with Alzheimer's disease and other dementias have more hospital stays, skilled nursing facility stays and home health care visits than other older people.

- *Hospital:* There are 780 hospital stays per 1000 Medicare beneficiaries age 65 and older with Alzheimer's disease and other dementias compared with 234 hospital stays per 1000 Medicare beneficiaries age 65 and older without these conditions [179]. The most common reasons for hospitalization of people with Alzheimer's disease are syncope (fainting), fall and trauma (26 percent); ischemic heart disease (17 percent); and gastrointestinal disease (9 percent) (Fig. 12) [331].
- *Skilled nursing facility:* Skilled nursing facilities provide direct medical care that is performed or supervised by registered nurses, such as giving intravenous fluids, changing dressings and administering tube feedings [332]. There are 349 skilled nursing facility stays per 1000 beneficiaries with Alzheimer's and other dementias compared with 39 stays per

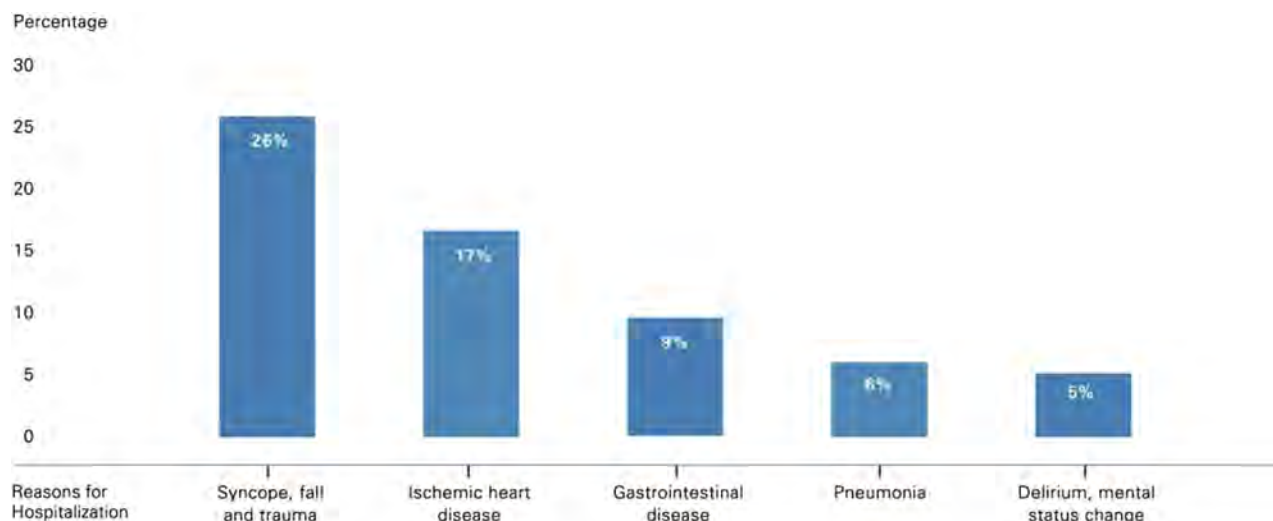


Fig. 12. Reasons for hospitalization of individuals with Alzheimer's disease: Percentage of hospitalized individuals by admitting diagnosis. All hospitalizations for individuals with a clinical diagnosis of probable or possible Alzheimer's disease were used to calculate percentages. The remaining 37 percent of hospitalizations were due to other reasons. Created from data from Rudolph and colleagues [331].

1000 beneficiaries for people without these conditions [179].

- **Home health care:** Twenty-three percent of Medicare beneficiaries age 65 and older with Alzheimer's disease and other dementias have at least one home health care visit during the year, compared with 10 percent of Medicare beneficiaries age 65 and older without Alzheimer's and other dementias [153].

Differences in health care use between individuals with and without dementia are most prominent for those residing in the community. Based on data from the Health and Retirement Study, community-residing individuals with dementia were more likely to have a potentially preventable hospitalization, an emergency department visit that was potentially avoidable, and an emergency department visit that resulted in a hospitalization [333]. For individuals residing in a nursing home, there were no differences in the likelihood of being hospitalized or having an emergency department visit.

Preventable hospitalizations are one common measure of health care quality. Preventable hospitalizations are hospitalizations for conditions that could have been avoided with better access to or quality of preventive and primary care. Based on data from the 2006 to 2008 Health and Retirement Study and Medicare, preventable hospitalizations represented 25 percent of the total hospitalizations for individuals with Alzheimer's disease and other dementias [334]. The proportion was substantially higher, however, for African-Americans, Hispanics and individuals with low incomes. Hispanic older adults had the highest proportion of preventable hospitalizations (34 percent). Healthy People 2020, the U.S. Department of Health and Human Services' initiative to achieve 10-year goals for health promotion and disease prevention, has set a target to reduce preventable hospitalizations

for people with Alzheimer's disease and other dementias by 10 percent by 2020 [334].

6.2.2. Costs of health care services

With the exception of prescription medications, average per-person payments for health care services (hospital, physician and other medical provider, nursing home, skilled nursing facility, hospice and home health care) were higher for Medicare beneficiaries with Alzheimer's disease and other dementias than for other Medicare beneficiaries in the same age group (Table 9) [179]. The fact that only payments for prescription drugs were lower for those with Alzheimer's and other dementias underscores the lack of effective treatments available to those with dementia.

Table 9

Average annual per-person payments for health care services provided to Medicare beneficiaries age 65 and older with and without Alzheimer's disease and other dementias, in 2014 dollars

Service	Beneficiaries with Alzheimer's disease and other dementias	Beneficiaries without Alzheimer's disease and other dementias
Inpatient hospital	\$11,370	\$4571
Medical provider*	6306	4181
Skilled nursing facility	4189	487
Nursing home	19,442	864
Hospice	1925	188
Home health	1543	498
Prescription medications†	2889	2945

NOTE. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008 [179].

*"Medical provider" includes physician, other medical provider and laboratory services, and medical equipment and supplies.

†Information on payments for prescription drugs is only available for people who were living in the community; that is, not in a nursing home or assisted living facility.

Table 10
Specific coexisting medical conditions among Medicare beneficiaries age 65 and older with Alzheimer's disease and other dementias, 2009

Coexisting condition	Percentage of beneficiaries with Alzheimer's disease and other dementias who also had coexisting medical condition
Coronary artery disease	30
Diabetes	29
Congestive heart failure	22
Chronic kidney disease	17
Chronic obstructive pulmonary disease	17
Stroke	14
Cancer	9

NOTE. Created from unpublished data from the National 20% Sample Medicare Fee-for-Service Beneficiaries for 2009 [153].

6.2.3. Use and costs of health care services for individuals newly diagnosed with Alzheimer's disease

Individuals newly diagnosed with Alzheimer's disease have higher health care use and costs in the year prior to diagnosis and in the 2 years after diagnosis than those who do not receive this diagnosis, according to a study of Medicare Advantage enrollees (that is, Medicare beneficiaries enrolled in a private Medicare health insurance plan) [335]. Enrollees with a new diagnosis of Alzheimer's disease had \$2529 more in health care costs (medical and pharmacy) in the year prior to diagnosis, \$10,126 more in costs in the year following diagnosis, and \$6251 more in costs in the second year following diagnosis. In another study of pre-diagnosis health care costs, Medicaid enrollees with Alzheimer's disease had \$6204 more in health care costs, with \$3713 due to additional outpatient medical care and \$1612 in additional home care and adult day care services [336].

While more work is needed to understand the underlying causes of increased use of health care services immediately prior to and after receiving a diagnosis of Alzheimer's disease, it may be attributed to care for disability and injuries, such as falls, that might result from the early stage of the disease [337]; treatments related to cognitive impairment or coexisting medical conditions; and costs of diagnostic procedures.

6.2.4. Impact of Alzheimer's disease and other dementias on use and costs of health care in people with coexisting medical conditions

Medicare beneficiaries with Alzheimer's disease and other dementias are more likely than those without dementia to have other chronic conditions [153]. Table 10 reports the proportion of people with Alzheimer's disease and other dementias who have certain coexisting medical conditions. In 2009, 30 percent of Medicare beneficiaries age 65 and older with dementia also had coronary artery disease, 29 percent also had diabetes, 22 percent also had congestive heart failure, 17 percent also had chronic kidney disease and 17 percent also had COPD [153].

People with Alzheimer's or other dementias and a serious coexisting medical condition (for example, congestive heart failure) are more likely to be hospitalized than people with the same coexisting medical condition but without dementia (Fig. 13) [153]. Research has demonstrated that Medicare beneficiaries with Alzheimer's disease and other dementias have more potentially avoidable hospitalizations for diabetes complications and hypertension, meaning that the hospitalizations could possibly be prevented through proactive care management in the outpatient setting [338].

Similarly, Medicare beneficiaries who have Alzheimer's and other dementias and a serious coexisting medical

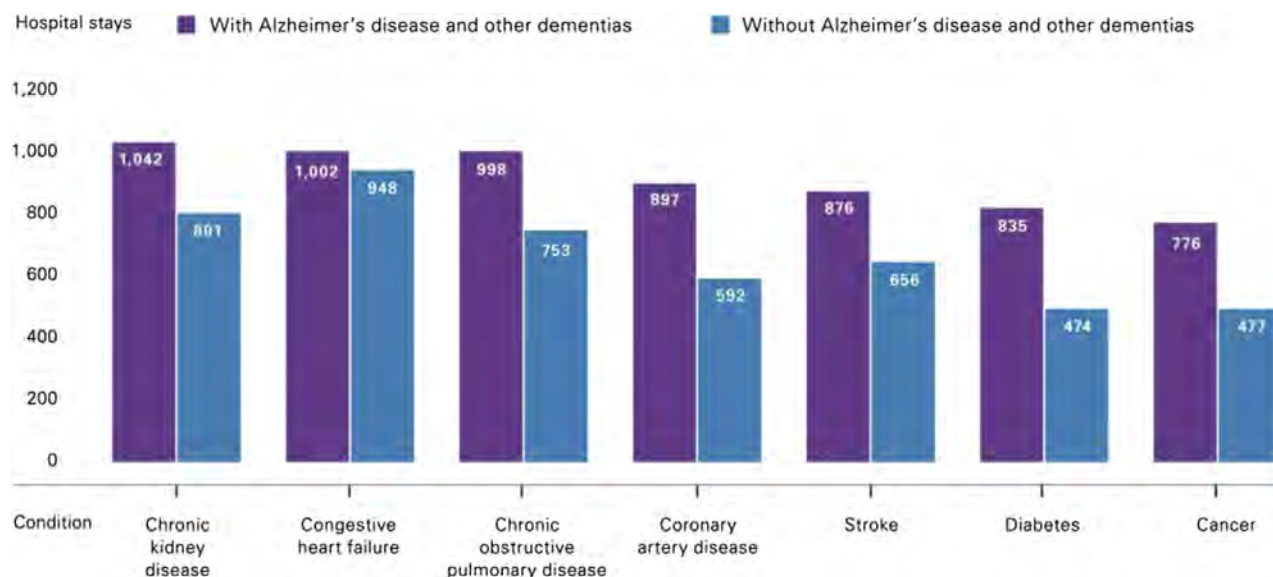


Fig. 13. Hospital stays per 1000 beneficiaries age 65 and older with specified coexisting medical conditions, with and without Alzheimer's disease and other dementias, 2009. Created from unpublished data from the National 20% Sample Medicare Fee-for-Service Beneficiaries for 2009 [153].

Table 11

Average annual per-person payments by type of service and coexisting medical condition for Medicare beneficiaries age 65 and older, with and without Alzheimer's disease and other dementias, 2009, in 2014 Dollars*

Medical condition by Alzheimer's disease/dementia (AD/D) status	Total Medicare payments	Average per-person Medicare payment				
		Hospital care	Physician care	Skilled nursing facility care	Home health care	Hospice care
Coronary artery disease						
With AD/D	27,661	10,225	1725	4433	2785	2403
Without AD/D	17,157	7347	1319	1351	1199	350
Diabetes						
With AD/D	26,994	9730	1615	4297	2869	2171
Without AD/D	14,920	5997	1136	1228	1137	246
Congestive heart failure						
With AD/D	26,509	11,613	1780	4915	2916	3014
Without AD/D	30,447	11,890	1779	2663	2297	852
Chronic kidney disease						
With AD/D	32,633	12,817	1910	4945	2722	2621
Without AD/D	25,108	10,743	1672	2040	1685	543
Chronic obstructive pulmonary disease						
With AD/D	30,007	10,914	1818	4845	2888	2714
Without AD/D	20,539	8953	1494	1766	1552	681
Stroke						
With AD/D	28,156	10,074	1675	4651	2639	2824
Without AD/D	20,214	7809	1425	2384	1936	668
Cancer						
With AD/D	25,910	9057	1573	3728	2274	2959
Without AD/D	16,957	6145	1207	1009	807	607

NOTE. Created from unpublished data from the National 20% Sample Medicare Fee-for-Service Beneficiaries for 2009 [153].

*This table does not include payments for all kinds of Medicare services, and as a result the average per-person payments for specific Medicare services do not sum to the total per-person Medicare payments.

condition have higher average per-person payments for most health care services than Medicare beneficiaries who have the same medical condition without dementia. Table 11 shows the average per-person Medicare payments for seven specific medical conditions among beneficiaries who have Alzheimer's disease and other dementias and beneficiaries who do not have dementia [153]. Medicare beneficiaries with dementia had higher average per-person payments in all categories except total Medicare and hospital care payments for individuals with congestive heart failure.

6.3. Use and costs of long-term care services

An estimated 58 percent of older adults with Alzheimer's disease and other dementias live in the community compared with 98 percent of older adults without Alzheimer's disease and other dementias [179]. Of those with dementia who live in the community, 75 percent live with someone and the remaining 25 percent live alone [179]. People with Alzheimer's disease and other dementias generally receive more care from family members and other unpaid caregivers as their disease progresses. Many people with dementia also receive paid services at home; in adult day centers, assisted living facilities or nursing homes; or in more than one of these settings at different times in the often long course of the disease. Given the high average costs of these services (assisted living, \$42,000 per year [339],^{A24} and nursing home care, \$77,380 to \$87,600 per year) [339],^{A24} individ-

uals often deplete their income and assets and eventually qualify for Medicaid. Medicaid is the only public program that covers the long nursing home stays that most people with dementia require in the late stages of their illnesses.

6.3.1. Use of long-term care services by setting

Most people with Alzheimer's disease and other dementias who live at home receive unpaid help from family members and friends, but some also receive paid home- and community-based services, such as personal care and adult day care. A study of older people who needed help to perform daily activities—such as dressing, bathing, shopping and managing money—found that those who also had cognitive impairment were more than twice as likely as those who did not have cognitive impairment to receive paid home care [340]. In addition, those who had cognitive impairment and received paid services used almost twice as many hours of care monthly as those who did not have cognitive impairment [340].

People with Alzheimer's and other dementias make up a large proportion of all elderly people who receive non-medical home care, adult day services and nursing home care.

- *Home care:* According to state home care programs in Connecticut, Florida and Michigan, more than one-third (about 37 percent) of older people who receive primarily non-medical home care services, such as personal care and homemaker services, have cognitive impairment consistent with dementia [341–343].

Table 12

Total nursing home beds and Alzheimer's special care unit beds by state, 2014

State	Total beds	Alzheimer's special care unit beds	Alzheimer's beds as a percentage of total beds
Alabama	26,338	1357	5.2
Alaska	693	37	5.3
Arizona	16,586	936	5.6
Arkansas	24,673	375	1.5
California	120,968	2556	2.1
Colorado	20,401	1967	9.6
Connecticut	27,673	1775	6.4
Delaware	4876	408	8.4
District of Columbia	2766	22	0.8
Florida	83,513	3922	4.7
Georgia	39,888	1362	3.4
Hawaii	4213	106	2.5
Idaho	5951	182	3.1
Illinois	99,389	4952	5.0
Indiana	60,107	5992	10.0
Iowa	34,213	1617	4.7
Kansas	25,751	159	0.6
Kentucky	26,779	741	2.8
Louisiana	35,533	1403	3.9
Maine	6981	349	5.0
Maryland	28,073	850	3.0
Massachusetts	48,376	3946	8.2
Michigan	46,594	789	1.7
Minnesota	30,362	2379	7.8
Mississippi	18,344	200	1.1
Missouri	55,294	4154	7.5
Montana	6708	534	8.0
Nebraska	15,943	959	6.0
Nevada	6016	270	4.5
New Hampshire	7491	710	9.5
New Jersey	52,310	1213	2.3
New Mexico	6814	529	7.8
New York	117,140	3791	3.2
North Carolina	44,849	1557	3.5
North Dakota	6153	449	7.3
Ohio	90,689	3751	4.1
Oklahoma	28,832	499	1.7
Oregon	12,263	274	2.2
Pennsylvania	88,261	6332	7.2
Rhode Island	8717	1202	13.8
South Carolina	19,631	64	0.3
South Dakota	6963	532	7.6
Tennessee	37,442	102	0.3
Texas	135,744	2583	1.9
Utah	8577	408	4.8
Vermont	3174	249	7.8
Virginia	32,453	1206	3.7
Washington	21,337	871	4.1
West Virginia	10,888	235	2.2
Wisconsin	34,060	2574	7.6
Wyoming	2984	312	10.5
U.S.	1,699,774	73,742	4.4

NOTE. Created from data from the American Health Care Association [349].

- *Adult day services*: Thirty-two percent of individuals using adult day services have Alzheimer's disease or other dementias [344], and 73 percent of adult day ser-

vices programs offer specific programs for individuals with Alzheimer's disease and other dementias [345].

- *Assisted living*: Forty-two percent of residents in assisted living facilities (that is, housing that includes services to assist with everyday activities, such as medication management and meals) had Alzheimer's disease and other dementias in 2010 [346]. Forty percent of residents in residential care facilities, including assisted living facilities, have Alzheimer's disease and other dementias [347]. Small residential care facilities (4 to 25 beds) have a larger proportion of residents with Alzheimer's and other dementias than larger facilities (49 percent versus 41 percent in facilities with 26 to 50 beds and 38 percent in facilities with more than 50 beds) [347]. Sixty-eight percent of residential care facilities offer programs for residents with Alzheimer's disease and other dementias, and 68 percent use a standardized tool to screen residents for cognitive impairment before or at admission [348].
- *Nursing home care*: Of all Medicare beneficiaries age 65 and older with Alzheimer's disease and other dementias, 31 percent live in a nursing home [179]. Of all Medicare beneficiaries residing in a nursing home, 64 percent have Alzheimer's disease and other dementias [179].
- *Alzheimer's special care units*: An Alzheimer's special care unit is a dedicated unit in a nursing home that has tailored services for individuals with Alzheimer's and other dementias. Nursing homes had a total of 73,742 beds in Alzheimer's special care units in 2014, a decrease of 3 percent from the previous year [349,350]. These Alzheimer's special care unit beds accounted for 71 percent of all special care unit beds and 4.4 percent of all nursing home beds. Rhode Island had the largest percentage of Alzheimer's special care unit beds as a proportion of total beds (13.8 percent), while Tennessee had the smallest percentage of Alzheimer's special care unit beds (0.3 percent) (Table 12) [349].

Recent research demonstrates that individuals with dementia often move between a nursing facility, hospital and home, rather than remaining in a nursing facility [351]. In a longitudinal study of primary care patients with dementia, researchers found that those discharged from a nursing facility were nearly equally as likely to be discharged home (39 percent) as discharged to a hospital (44 percent). Individuals with dementia may also transition between a nursing facility and hospital or between a nursing facility, home and hospital, creating challenges for caregivers and providers to ensure that care is coordinated across settings. Other research has shown that nursing home residents frequently have burdensome transitions at the end of life, including admission to an intensive care unit in the last month of life, late enrollment in

hospice and receipt of a feeding tube [352]. The number of care transitions for nursing home residents with advanced cognitive impairment varies substantially across geographic regions of the United States [353]. Researchers also found that both the number of transitions between health care settings and the odds of having a feeding tube inserted at the end of life varied across the country. Furthermore, individuals with frequent transitions between health care settings were more likely to have feeding tubes at the end of life, even though feeding tube placement has little or no benefit. These differences across geographic regions were not explained by severity of illness, restrictions on the use of artificial hydration and nutrition, ethnicity or gender, and may reflect differences in the quality of care, although more research is needed. Additionally, researchers found that feeding tube use was highest for people with dementia whose care was managed by a subspecialist physician or both a subspecialist and a general practitioner. Feeding tube use was lower among people with dementia whose care was managed by a general practitioner [354].

Research has also demonstrated a decrease in the proportion of individuals with Alzheimer's disease who die in an acute care hospital, with end-of-life care shifting to home and nursing homes [355]. Additionally, more than twice as many individuals with the disease were receiving hospice care at the time of death in 2009 than in 2000 (48 percent in 2009 versus 20 percent in 2000).

Demands for nursing home services and services from long-term care hospitals are increasing. Long-term care hospitals serve individuals whose acute medical conditions require long-term care. Individuals are often transferred from the intensive care units of acute care hospitals to long-term care hospitals for medical care related to rehabilitation services, respiratory therapy and pain management. Despite this increasing demand, there have been a number of restrictions on adding facilities and increasing the number of beds in existing facilities. In addition, the Medicare, Medicaid and SCHIP (State Children's Health Insurance Program) Extension Act of 2007 issued a 3-year moratorium on both the designation of new long-term care hospitals and increases in Medicare-certified beds for existing long-term care hospitals [356]. This moratorium was in response to the need for Medicare to develop criteria for admitting beneficiaries to long-term care hospitals, where stays average more than 25 days [357]. The moratorium expired in late 2012 [356,358]. In 2011, certificate-of-need programs (i.e., programs that require approval before building new facilities and/or expanding beds or other services) were in place in 37 states to regulate the number of nursing home beds, and a number of these states had implemented a certificate-of-need moratorium to prevent growth in the number of beds and/or facilities [359].

6.3.2. Costs of long-term care services

Costs are high for care provided at home or in an adult day center, assisted living facility or nursing home. The following estimates are for all users of these services.

- *Home care:* The median cost for a paid non-medical home health aide is \$20 per hour, or \$160 for an eight-hour day [339].^{A24}
- *Adult day centers:* The median cost of adult day services is \$65 per day [339].^{A24} Ninety-five percent of adult day centers provided care for people with Alzheimer's disease and other dementias, and 2 percent of these centers charged an additional fee for these clients in 2012 [360].
- *Assisted living facilities:* The median cost for basic services in an assisted living facility is \$3500 per month, or \$42,000 per year [339].^{A24}
- *Nursing homes:* The average cost for a private room in a nursing home is \$240 per day, or \$87,600 per year. The average cost of a semi-private room in a nursing home is \$212 per day, or \$77,380 per year [339].^{A24}

6.3.3. Affordability of long-term care services

Few individuals with Alzheimer's disease and other dementias have sufficient long-term care insurance or can afford to pay out of pocket for long-term care services for as long as the services are needed.

- Income and asset data are not available for people with Alzheimer's and other dementias specifically, but 50 percent of Medicare beneficiaries had incomes of \$23,983 or less, and 25 percent had incomes of \$14,634 or less in 2013 (in 2014 dollars) [361].
- Fifty percent of Medicare beneficiaries had total savings of \$62,396 or less, 25 percent had savings of \$11,483 and 8 percent had no savings or were in debt in 2013 (in 2014 dollars). Median savings were substantially lower for African-American and Hispanic Medicare beneficiaries than white Medicare beneficiaries [361].

6.3.4. Long-term care insurance

Enrollment in private long-term care insurance is more common for older adults with higher-than-average incomes. While only 3 percent of adults age 55 and older had long-term care insurance in 2008, 19 percent with incomes greater than \$100,000 had long-term care insurance [362]. The average annual long-term care insurance premium was \$2320 in 2010 [362]. Private health [363] and long-term care insurance policies funded only about 7 percent of total long-term care spending in 2011, representing \$25 billion of the \$363 billion in long-term care spending [364]. The private long-term care insurance market has consolidated since 2010. Five major insurance carriers either exited the market or substantially increased

premiums since then, making policies unaffordable for many individuals [365].

6.3.5. Medicaid costs

Medicaid covers nursing home care and long-term care services in the community for individuals who meet program requirements for level of care, income and assets. To receive coverage, beneficiaries must have low incomes. Most nursing home residents who qualify for Medicaid must spend all of their Social Security income and any other monthly income, except for a very small personal needs allowance, to pay for nursing home care. Medicaid only makes up the difference if the nursing home resident cannot pay the full cost of care or has a financially dependent spouse.

The federal and state governments share in managing and funding the program, and states differ greatly in the services covered by their Medicaid programs. Medicaid plays a critical role for people with dementia who can no longer afford to pay for long-term care expenses on their own. In 2011, 55 percent of Medicaid spending on long-term care was allocated to institutional care, and the remaining 45 percent was allocated to home and community-based services [364].

Total Medicaid spending for people with Alzheimer's disease and other dementias is projected to be \$41 billion in 2015 (in 2015 dollars).^{A20} Total per-person Medicaid payments for Medicare beneficiaries age 65 and older with Alzheimer's and other dementias were 19 times as great as Medicaid payments for other Medicare beneficiaries. Much of the difference in payments for beneficiaries with Alzheimer's and other dementias is due to the costs associated with long-term care (nursing homes and other residential care facilities, such as assisted living facilities) and the greater percentage of people with dementia who are eligible for Medicaid. Medicaid paid an average of \$26,086 per person for Medicare beneficiaries with Alzheimer's and other dementias living in a long-term care facility compared with \$242 for those with the diagnosis living in the community and an average of \$574 for older adults without the diagnosis living in the community and long-term care facilities (Table 8) [179].

In a study of Medicaid beneficiaries with a diagnosis of Alzheimer's disease, researchers found significant differences in the cost of care by race/ethnicity [366]. These results demonstrated that African-Americans had significantly higher cost of care than whites or Hispanics, primarily due to more inpatient care and greater severity of illness. These differences may be attributable to later-stage diagnosis, which may lead to higher levels of disability while receiving care; delays in accessing timely primary care; lack of care coordination; and duplication of services across providers. However, more research is needed to understand the reasons for this health care disparity.

6.3.6. Programs to reduce avoidable health care and nursing home use

Recent research has demonstrated that two different types of programs have potential for reducing avoidable health care and nursing home use, with one type of program focusing on the caregiver and the other type of program focusing on the care delivery team.

Studies of the effectiveness of caregiver support programs suggest that these programs have promise for reducing unnecessary emergency department visits and hospitalizations and reducing transitions to residential care for individuals with Alzheimer's disease and other dementias. For example, in an evaluation of the Dementia Care Services Program in North Dakota, researchers found that hospitalizations, ambulance use, emergency department visits and 911 calls decreased significantly after caregivers began working with the program, which offered them care consultations, resources and referrals [367]. In another study, researchers estimated the effects of applying the New York University Caregiver Intervention on health care costs and utilization in the state of Minnesota over 15 years. They determined that this intervention, which includes individual and family caregiver counseling sessions, an ongoing weekly caregiver support group and telephone counseling, would increase the number of individuals with dementia able to continue residing in the community by 5 percent. They also predicted that nearly 20 percent fewer individuals with dementia would die in residential care [368], and that the reduced number of transitions to residential care would lower health care costs in Minnesota by \$996 million over the 15-year period. More research is needed to determine the extent to which these results apply to the broader population of individuals with Alzheimer's disease and other dementias and their caregivers.

Additionally, collaborative care models—models that include not only geriatricians, but also social workers, nurses and medical assistants—improve care coordination, thereby reducing health care costs associated with hospitalizations, emergency department visits and other outpatient visits [369]. An interprofessional memory care clinic was shown to reduce per-person health care costs by \$3474 over a year for individuals with memory problems, compared with others whose care was overseen by a primary care provider only [369]. More than half of the cost savings was attributed to lower inpatient hospital costs. The program was relatively low cost per person, with an average annual cost of \$618 [369].

6.4. Use and costs of hospice care

Hospice care provides medical care, pain management and emotional and spiritual support for people who are dying, including people with Alzheimer's disease and other dementias. Hospice care also provides emotional and spiritual support and bereavement services for families of people who are dying. The main purpose of hospice is to allow

individuals to die with dignity and without pain and other distressing symptoms that often accompany terminal illness. Individuals can receive hospice care in their homes, assisted living residences or nursing homes. Medicare is the primary source of payment for hospice care, but private insurance, Medicaid and other sources also pay for hospice care.

In 2009, 6 percent of people admitted to hospices in the United States had a primary hospice diagnosis of Alzheimer's disease (61,146 people) [370]. An additional 11 percent of those admitted to hospices in the United States had a primary hospice diagnosis of non-Alzheimer's dementia (119,872 people) [370]. Hospice length of stay has increased over the past decade. The average length of stay for hospice beneficiaries with a primary hospice diagnosis of Alzheimer's disease increased from 67 days in 1998 to 106 days in 2009 [370]. The average length of stay for hospice beneficiaries with a primary diagnosis of non-Alzheimer's dementia increased from 57 days in 1998 to 92 days in 2009 [370]. Average per-person hospice care payments for beneficiaries with Alzheimer's disease and other dementias were 10 times as great as for all other Medicare beneficiaries (\$1925 per person compared with \$188 per person) [179].

6.5. Projections for the future

Total annual payments for health care, long-term care and hospice care for people with Alzheimer's disease and other dementias are projected to increase from \$226 billion in 2015 to more than \$1 trillion in 2050 (in 2015 dollars). This dramatic rise includes a five-fold increase in government spending under Medicare and Medicaid and a nearly five-fold increase in out-of-pocket spending.^{A20}

7. Special report: Disclosing a diagnosis of Alzheimer's disease

Should health care providers always tell their patients about a diagnosis? When, if ever, is it acceptable to keep the diagnosis from the patient, or to soften its impact by using less-than-clear explanations?

A limited number of studies have explored whether people who had been diagnosed with Alzheimer's disease or another dementia could recall being told their diagnosis [371–374]. The studies often found that fewer than 50 percent of patients recalled being told their diagnosis. The factors affecting whether individuals are told their diagnosis are numerous and complex. Understanding and addressing these factors may improve the care that patients receive, their ability to cope with the diagnosis, and their relationships with family members and caregivers.

7.1. Historical context

In the 1950s and early 1960s, the issue of whether to tell cancer patients about their diagnosis was much discussed. In

one study published in 1961, a group of 291 physicians who treated cancer patients were asked about their usual policies regarding disclosure of a cancer diagnosis to the patient [375]. Almost 9 in 10 (88 percent) responded that it was their usual policy to *not* tell patients that they had been diagnosed with cancer. Reasons for not telling were varied but generally focused on the desire to protect the patient from harm and preserve hope. Many physicians thought that disclosing the diagnosis could cause the patient unnecessary anxiety or depression or lead to thoughts of suicide. However, there was very little evidence that such concerns were justified.

Physicians also had the common perception that cancer treatments available in 1961 were ineffective, so there was no benefit to revealing the diagnosis [375]. The survey even revealed that many physicians at the time opposed research into how patients react to such disclosures. Fortunately, much research was done and principles of disclosure have now been elaborated and taught. Furthermore, the benefits of disclosure to patients have been recognized, and today nearly all health care providers have the usual policy of disclosing a cancer diagnosis to patients and accurately explaining prospects for the future [376].

The principles guiding disclosure of a cancer diagnosis apply equally to other diagnoses. But there is evidence that these principles are not always applied in practice, especially when the diagnosis involves conditions affecting the brain. As this report will show, it is still common for patients and their caregivers to not be made aware of a diagnosis of Alzheimer's disease or dementia, or to be left with insufficient understanding of the true nature of the diagnosis.

7.2. A consensus for disclosure

Health care providers routinely encounter the situation of having to deliver a frightening or upsetting diagnosis to patients and perhaps to relatives, friends and loved ones. Like the practice of medicine itself, the ethical principles guiding health care providers during such encounters have evolved during the last half century, and today there is general agreement that patients have the right to know and understand their diagnosis.

Several professional organizations working in the realm of brain health have issued statements regarding the disclosure of a diagnosis of Alzheimer's disease or another dementia. These include the Alzheimer's Association [377], Alzheimer Europe [378], the American [379] and Canadian Medical Associations [380], the American Psychiatric Association [381], the European Federation of Neuroscience Societies [382] and other organizations [383,384]. Guidelines uniformly advocate revealing the diagnosis to the person who has been diagnosed and doing so in clear language. Guidance from the Alzheimer's Association, for example, advocates talking to the affected person directly and delivering the news in "plain but sensitive language" [377]. However, almost all such guidelines recognize that there may be situations in which communicating the diagnosis to the

patient is not possible or practicable. Furthermore, some individuals may prefer to not be told, and that preference must be taken into account. However, a person with Alzheimer's or another dementia—especially in the later stages of disease—should have an informed and cognitively intact caregiver to ensure their safety and appropriate care.

The widespread agreement among professionals that people with Alzheimer's disease or another dementia should be told of their diagnosis is founded upon general principles of medical ethics, as well as research into the benefits and potential harms of such disclosure. Two ethical principles that have perhaps the strongest bearing on this issue are respect for patient autonomy and truth-telling.

7.2.1. *Respect for patient autonomy*

People have the right to make decisions about their medical care, including mental health care [385]. One aspect of this principle is that patients have the right to decide whether they want to be told their diagnosis. But there are caveats. First, decisions should be made from an informed perspective [386]. Patients should understand the potential benefits and drawbacks of each decision, including the decision of whether to be told their diagnosis. For example, not receiving the diagnosis may deprive patients of the opportunity to seek other medical opinions, plan for the future, and be involved in decisions that could impact their health care both now and in the future. Second, a person who does not have the mental capacity to understand their condition or treatment choices cannot give informed consent to treatment. In such cases, decisions are usually made by a person representing the patient's best interests. Unfortunately, accurately assessing a patient's ability to understand the diagnosis and treatment options can be challenging for the health care provider [386]. In Alzheimer's, those abilities may remain consistent for an extended period or change from day to day, or even hour to hour [387,388]. Furthermore, when decision-making responsibilities are given to a caregiver, the wishes of the caregiver may not match those of the person diagnosed. Several studies have shown, for example, that caregivers do not want care recipients to be told about a diagnosis of Alzheimer's disease or another dementia, even though the caregivers would want to be told if they were the ones being diagnosed [389,390].

7.2.2. *Truth-telling*

It was common in the past to withhold from patients the truth about the nature or severity of their illness. One reason that has frequently been given for withholding the truth is fear of causing distress or of taking away hope [390]. Research conducted in recent decades has dispelled many of these concerns, showing that most people are able to cope with knowing about their condition and that there are many benefits to patients being fully informed. It is now widely recognized that truth-telling in medical diagnosis should be the standard approach, and that more harm than good often comes from not telling patients the truth [385].

Withholding the truth can lead to loss of trust and cooperation among patients, family members and health care providers, and it can actually worsen the distress associated with the diagnosis [384,391–393].

7.3. *Are people being told they have Alzheimer's by their health care providers?*

Several studies have found that a large majority of physicians and other health care providers recognize the benefits of disclosing the diagnosis of Alzheimer's disease or another dementia [394]. Despite these findings and the existence of guidelines strongly advocating disclosure of the diagnosis, health care providers vary widely in their practices regarding disclosure [390,394–397]. In fact, one of the goals of the federal government's Healthy People 2020 program is to increase awareness of the diagnosis of Alzheimer's disease and other dementias among those who have been diagnosed or their caregivers [374].

To explore recent disclosure practices, the Alzheimer's Association commissioned an analysis of Medicare records and responses to the Medicare Current Beneficiary Survey (MCBS), a continuous survey of a nationally representative sample of Medicare beneficiaries living in the community or in long-term care facilities. About 16,000 Medicare beneficiaries complete the survey in any given year, and an individual respondent typically participates in the survey for several consecutive years. The Centers for Medicare and Medicaid Services maintain a database of medical claims submitted by health care providers for care provided to all Medicare beneficiaries.

In the current analysis, de-identified claims records were analyzed for all people who participated in the MCBS during 2008, 2009 and 2010. These records were used to identify individuals with at least one claim related to selected medical conditions, including Alzheimer's disease, other forms of dementia, breast cancer, prostate cancer, lung cancer, colorectal cancer,^{A25} stroke, cardiovascular disease other than stroke, Parkinson's disease, diabetes, arthritis, high blood pressure and high cholesterol. (Claims were used to indicate that the person's health care provider had given care because of an indicated medical condition.) Responses on the MCBS were then analyzed to determine whether the respondent indicated that they had been told by their doctor that they had the indicated conditions. For example, a Medicare beneficiary with a claim that indicated a diagnosis of Alzheimer's disease would be asked, "Has a doctor ever told you that you have Alzheimer's disease?" When the beneficiary was unavailable or unable to answer the question, a similar question was posed to a proxy respondent (often a family member or caregiver). Similarly, respondents with a claim related to breast cancer had that claim linked to their MCBS response as to whether a doctor had ever told them they had cancer.

From these data, a disclosure rate was calculated to determine the percentage of respondents with a specified medical

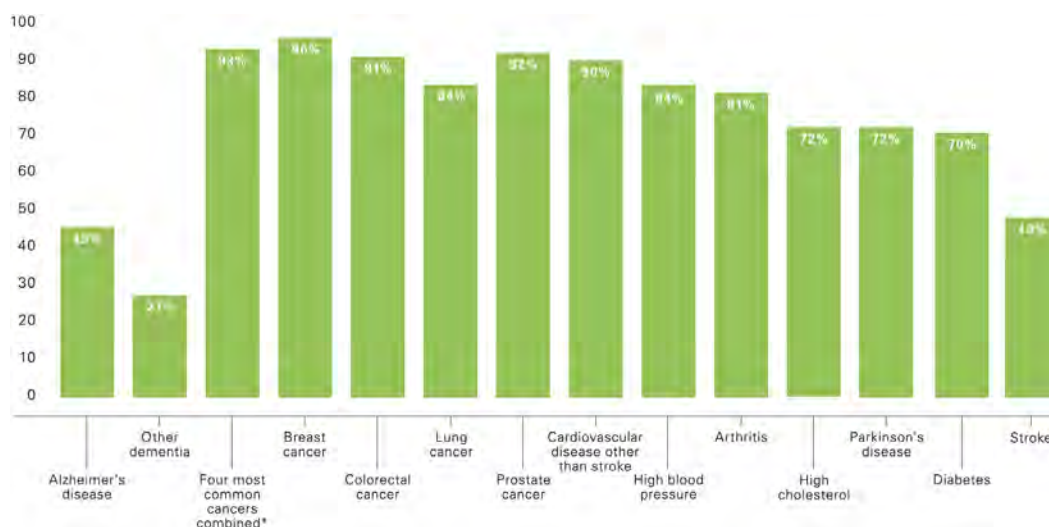


Fig. 14. Disclosure rates among MCBS respondents for the indicated medical conditions. *Breast, colorectal, lung and prostate cancer. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008, 2009 and 2010 and Medicare claims data.^{A27} Values shown are weighted to adjust the demographics of the responding sample population to match the demographics of the U.S. population.

condition claim who indicated that their doctor had told them they had that medical condition.^{A26}

Disclosure rates for several common medical diagnoses are shown in Fig. 14.^{A27} The disclosure rate for Alzheimer's disease was 45 percent. The disclosure rate was even lower (27 percent) among those diagnosed with other conditions that cause dementia. In contrast, disclosure rates were substantially higher for all other conditions studied except stroke. For example, among respondents with a Medicare claim for one of the four most common cancers (cancer of the breast, colon or rectum, lung and prostate), 93 percent reported being told of their diagnosis. With the exception of stroke (48 percent), disclosure rates were significantly lower for people with a diagnosis of Alzheimer's disease or another dementia than for those with other diagnoses.^{A28}

These data suggest that people with Alzheimer's disease or another dementia are much less likely to be told about the diagnosis by their doctors or health care providers than people with other common medical conditions. This finding is consistent with several older studies in which generally fewer than 50 percent of patients with Alzheimer's disease or dementia reported being told their diagnosis [371–373,398]. The results are also comparable with those of a more recent analysis by the U.S. Centers for Disease Control and Prevention, which found that among people with Alzheimer's disease or another dementia, they or their caregivers reported being aware of the diagnosis in only 35 percent of cases [374].

Previous studies have also explored the attitudes and practices of health care providers regarding the disclosure of a diagnosis of Alzheimer's disease or dementia. Practices varied widely, with 38 percent to 96 percent of health care providers reporting that they usually disclose the diagnosis to the person with Alzheimer's or dementia [394].

Many studies report that health care providers were more likely to disclose the diagnosis to caregivers than to affected persons, with 64 percent to 100 percent of health care providers reporting they disclose the diagnosis to caregivers [394,398]. The current analysis also explored this possibility. Fig. 15 shows the responses according to whether the respondent was the Medicare beneficiary or a proxy respondent. Notably, when people with Alzheimer's disease or another dementia were asked if a doctor had told them they had the disease, only about one in three (33 percent) and one in five (18 percent), respectively, responded "Yes." However, when the respondent was a proxy, they were more likely to report having been told that the beneficiary had been diagnosed with Alzheimer's disease or another dementia (53 percent and 50 percent, respectively). The reason for this difference between beneficiary and proxy respondents is unclear; however, even in the best case scenario, the disclosure rate is barely more than half of cases. Other diagnoses involving brain conditions, such as stroke and Parkinson's disease, also showed differences between beneficiaries and proxy respondents, although the differences were not as prominent as for Alzheimer's and other dementias. One complicating factor in these results is that people with severe Alzheimer's or another dementia are more likely to have proxy respondents than people in earlier stages. Thus, the greater disclosure rates reported by proxy respondents compared with beneficiary respondents could be due to the presence of more severe disease in people who required proxy respondents.

In the current analysis commissioned by the Alzheimer's Association, several factors were explored to determine if they influenced whether respondents reported that a doctor had told beneficiaries about their diagnosis of Alzheimer's disease or another dementia. Factors included the beneficiary's age, sex, race or ethnicity, income level, education

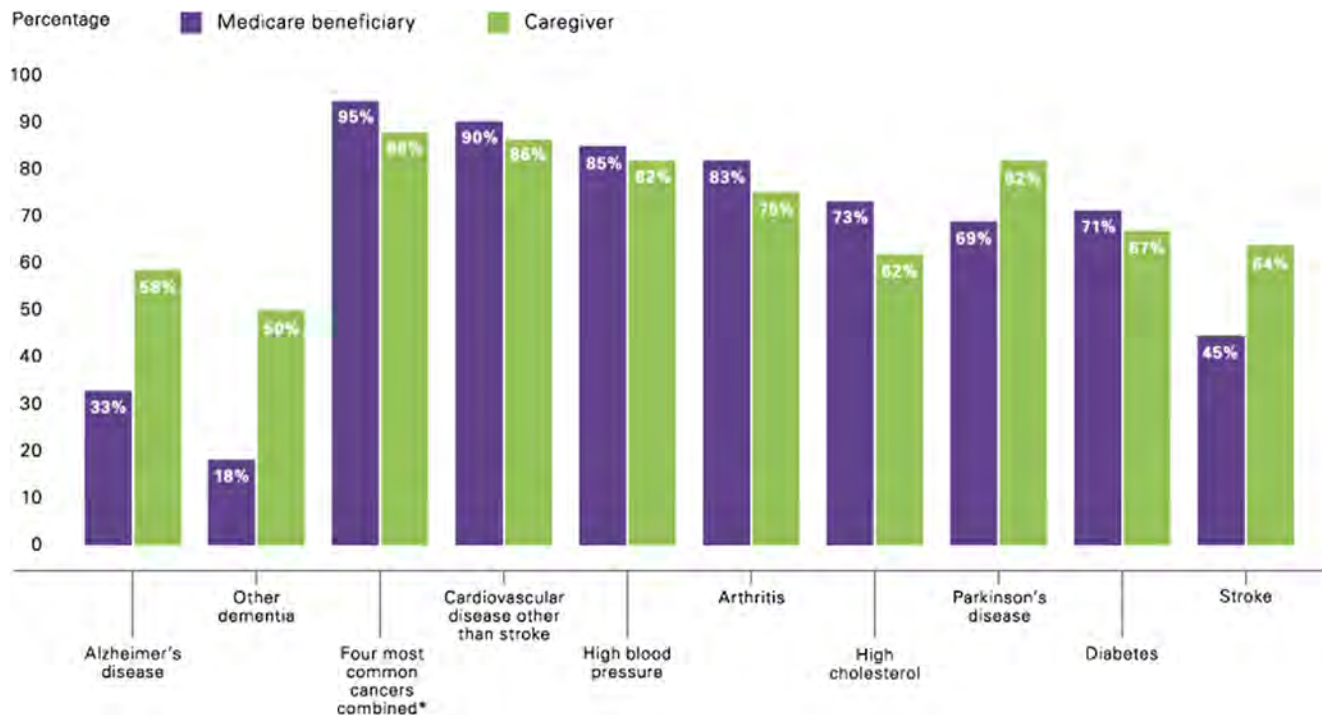


Fig. 15. Disclosure rates according to whether the respondent was a beneficiary or a caregiver. *Breast, colorectal, lung, and prostate cancer. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008, 2009 and 2010 and Medicare claims data.^{A27}

level, geographic region, and the patient's degree of impairment as assessed by the number of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) for which the person needed assistance. Disclosure rates consistently and significantly varied according to only two of these factors—the number of ADLs and IADLs for which the person needed assistance (Figs. 16 and 17).^{A29}

Activities of daily living are those self-care activities that are fundamental to day-to-day life, including walking, getting into and out of bed, bathing, dressing, toileting and

eating. Instrumental ADLs are less fundamental to daily living, but still promote the ability to lead an independent lifestyle. These include such activities as housework, shopping, managing one's own prescribed medications, using the phone or other forms of communication, and taking care of transportation within the community, such as driving or using public transit.

As shown in Figs. 16 and 17 for ADLs and IADLs, respectively, when the beneficiary had more severe disability, they or their proxy were more likely to report

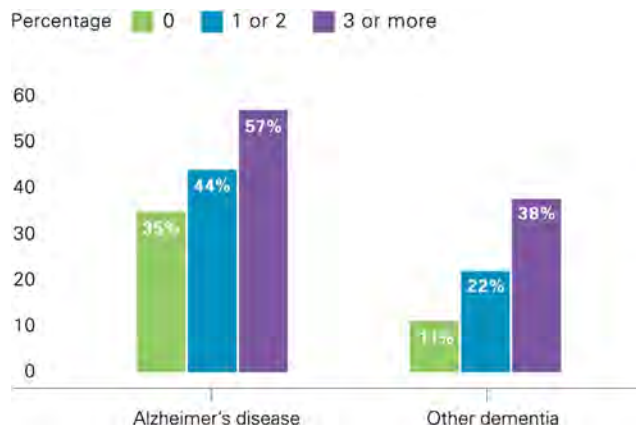


Fig. 16. Disclosure rates according to the beneficiary's degree of disability as determined by the number of ADLs for which assistance was needed. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008, 2009 and 2010 and Medicare claims data.^{A27}

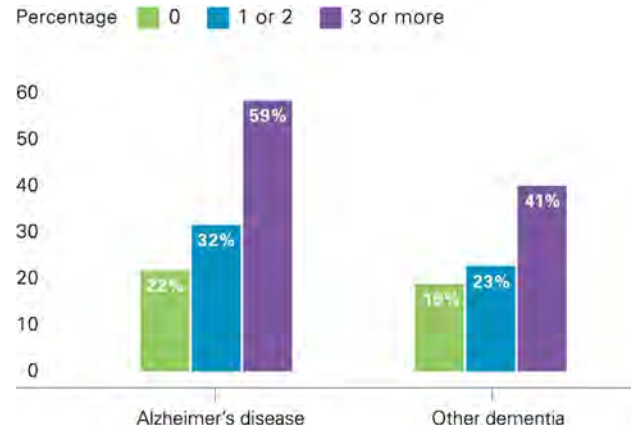


Fig. 17. Disclosure rates according to the beneficiary's degree of disability as determined by the number of IADLs for which assistance was needed. Created from unpublished data from the Medicare Current Beneficiary Survey for 2008, 2009 and 2010 and Medicare claims data.^{A27}

being told of the diagnosis of Alzheimer's disease or dementia than when the beneficiary had less severe disability. These findings may indicate that health care providers are more likely to disclose the diagnosis when disability is more severe. It also may be a consequence of the fact that patients with more severe disability have had the disease longer and, therefore, have had more opportunities for the diagnosis to be disclosed to them. Previous studies have had conflicting results regarding whether patients with mild disease are more or less likely to be told their diagnosis than patients with more severe disease [399–401]. In some situations, health care providers may choose not to directly disclose the diagnosis to people with severe disease because such patients are not likely to understand or remember [390]. In other situations, there is sometimes greater reluctance to reveal the diagnosis to someone who has mild disease because of fear about how they may react [398].

7.3.1. Some caveats

One problem common to many studies of people with Alzheimer's disease and other causes of dementia is that the diseases themselves may affect the ability of the affected people to remember being told their diagnosis. The current analysis argues against this explanation because disclosure rates were higher among beneficiaries with more severe disability (as measured by the number of ADLs and IADLs for which they needed assistance) than beneficiaries with less severe disability. In addition, even the proxy respondent numbers are very low—only about 50 percent—so it is unlikely that inability to recall disclosure is a significant factor.

However, studies have found that a large percentage of people with dementia and even some caregivers were unable to accurately recall the diagnosis soon after being told [371,373]. This underscores the need for continued efforts by health care providers to ensure that the diagnosis is disclosed fully and carefully. Another problem is that some patients and even some caregivers may deny the diagnosis or use denial as a way to cope with the diagnosis [402]. Using only the data shown here, it is not possible to determine how many people may have reported not being told of their diagnosis because of denial or failure to accurately remember being told.

7.4. Reasons cited for not disclosing a diagnosis

MCBS data do not contain information about why people are not told of their diagnosis, but numerous studies have explored this issue from the perspectives of health care providers, caregivers and people with Alzheimer's or another dementia [376,395,396].

- *Diagnostic uncertainty:* Health care providers frequently cite the complexity and uncertainty of the diagnosis as one barrier to disclosure [125,376,403]. A further complication is that diagnostic uncertainty may prompt referral to a specialist, which itself may reveal the suspicion of Alzheimer's or dementia. Ongoing efforts are focused on developing educational programs for health care providers to improve their diagnostic skills related to dementia [404].
- *Time constraints and lack of support:* Disclosing a diagnosis of Alzheimer's or another dementia to a patient usually requires discussion of treatment options and support services, as well as education about the disease and what to do. In many health care settings, providers have insufficient time to dedicate to such activities [403]. Physicians and other health care providers have also noted that there are insufficient resources and services, including insufficient geriatric specialists and interdisciplinary teams, to provide patients and caregivers with the support needed at the time of diagnosis and afterward [405].
- *Communication difficulties:* Many providers find that disclosure of the diagnosis is one of the most challenging aspects of the diagnostic process [396,403], and there have been calls for educational programs to improve the communication skills of providers to address this barrier [405,406]. Providers may also be concerned about whether disclosure of the diagnosis will be understood and accepted by patients or caregivers [371,373,390].
- *Fear of causing emotional distress:* This is one of the reasons most commonly cited by family members and health care providers for not disclosing the diagnosis or for disguising its true nature [390]. However, studies that have explored this issue have found that few patients become depressed or have other long-term emotional problems because of the diagnosis [401,407–409]. One study concluded that “physicians can provide a suspected dementia diagnosis without fear of prompting a catastrophic emotional reaction in most individuals with early-stage dementia” [410]. Although there has been fear of suicide, the evidence indicates that it is very uncommon [411]. Certainly, many patients experience initial shock, fear, distress, anger or other emotions, but true clinical depression is uncommon [393,409,410]. In one study, only 6 percent of people diagnosed with Alzheimer's disease or another dementia had clinical depression after 1 year, and those requiring treatment for depression were likely to have had a history of depression [393].
- *Patient or caregiver wishes:* Studies have shown that most patients want to be told if they have been diagnosed with Alzheimer's or another dementia, but some patients prefer not to be told. Although most caregivers support disclosure of the diagnosis to the patient [390,396], sometimes family members and caregivers request that the patient not be told [389,390]. These requests usually stem from concern that the affected person will have a distressing emotional response to the disclosure. Such requests can create a

dilemma for providers, who must choose between respecting the patient's autonomy or the wishes of caregivers and family members. Recent guidance generally advocates for holding the patient's wishes as the highest priority [412].

- *Lack of disease-modifying treatment:* In one study, 25 percent of health care providers indicated that the lack of treatments to modify the course of disease was a factor in choosing not to disclose a diagnosis to patients [390]. However, informed patients and caregivers have better access to support services, are more able to participate in decision-making, and are better able to adapt to the diagnosis.
- *Stigma:* The stigma experienced by some people diagnosed with Alzheimer's disease or another dementia is very real and can have detrimental consequences [413]. The stigma can vary widely between cultures. In one study conducted in Italy, some caregivers expressed the opinion that it was disrespectful for a health care provider to tell an older person that they had dementia [384]. In other cultural settings, patients expressed the sense that their friends afforded them less esteem after the diagnosis than before [413]. Patients may even attach a stigma to their own diagnosis, viewing a diagnosis of Alzheimer's or another dementia differently than they would other "physical" conditions, even though the symptoms of Alzheimer's and other dementias are manifestations of physical changes in the brain. As a consequence, it is common for patients to disguise their symptoms from family members and health care providers and to avoid discussing memory problems [413]. Similarly, health care providers may avoid the issue to spare the patient from a potentially stigmatizing diagnosis [413].

7.5. Benefits of disclosing a diagnosis of Alzheimer's disease or other dementia

Several studies have found benefits to promptly and clearly explaining a diagnosis of dementia to the affected person and that person's caregiver(s) [376,395,396,407].

- *Better diagnosis:* When a patient understands their diagnosis, they have the opportunity to seek other medical opinions or the advice of specialists. The decision to withhold the diagnosis rests on the assumption that the diagnosis is correct. However, several reversible conditions can mimic dementia, including depression, thyroid dysfunction, vitamin deficiency and sleep disruption [414]. Concern about having to tell a patient that they have Alzheimer's disease or another dementia has been cited as one barrier to early diagnosis [405]. However, early diagnosis is associated with numerous benefits regardless of whether a treatment is available [414].
- *Better decision-making:* When a patient is fully aware of their diagnosis in the early stages of the disease, the

patient is likely to be competent to understand options and provide informed consent for current and future treatment options, including participation in research studies. In this way, the affected person can ensure that their desires and preferences are known, which may help them get better medical care and may contribute to advancing research toward better treatments [399,407]. Furthermore, when people are actively involved in decision-making about their care, they are more likely to follow a treatment plan and take steps to maintain their health.

- *Better medical care:* Studies have shown that when patients understand their diagnosis and are active participants in the decision-making process, the quality of care they receive is better than the care received by uninformed patients [415–417].
- *Respect for the patient's wishes:* Although studies of the opinions and attitudes of patients with memory complaints are limited, the evidence indicates that most patients with mild dementia want to be told their diagnosis [393,396,418].
- *Planning for the future:* Prompt disclosure of the diagnosis allows patients and caregivers to get legal and financial affairs in order with the full and informed consent of the affected person.
- *Understanding changes:* People affected by memory loss and their caregivers are often aware that something is not right. Knowing the diagnosis can help them understand the symptoms they have felt or observed. Among caregivers, knowledge of the diagnosis and disease characteristics can help them better appreciate their loved one's remaining capacities [401].
- *Coping:* Although the initial disclosure can be shocking, distressing or embarrassing, being aware of the diagnosis gives patients and their caregivers the opportunity to express their fears and grief and to adopt positive strategies for coping with the diagnosis [401,407]. Health care professionals are frequently concerned that patients and their caregivers will lose hope or become depressed when they learn of the diagnosis, but several studies have found these concerns to be unwarranted or overemphasized [394]. Some patients and caregivers express relief when they finally know the diagnosis; it removes uncertainty and gives them the opportunity to develop a plan of action [410]. Some caregivers have expressed that knowing the diagnosis allows them to blame the disease for changes in their loved one's behavior, rather than blaming the person. Knowing the diagnosis can also help caregivers prepare for and adapt to their role [401], which can reduce the perceived burden of caregiving [419].
- *Access to services:* Knowing the diagnosis allows patients and caregivers to obtain information about support services and make plans to use such services. Accessing support services can help patients and

caregivers cope with the diagnosis and behavior changes that may accompany it [401,418].

- *Safety*: Awareness of the diagnosis allows caregivers to take steps to ensure the affected person's environment is safe and may help caregivers take precautionary steps to determine when certain activities (such as driving) may need to be curtailed.
- *Social support*: Knowing the diagnosis helps affected people focus on spending quality time with loved ones, garnering social support, appreciating what life has to offer and possibly traveling or fulfilling long-held wishes.

7.6. The process of disclosure

The analysis described in this report gives only a snapshot of whether patients or caregivers report being told by a doctor that they or a care recipient have Alzheimer's disease or another dementia. Just as important is *how* the diagnosis is disclosed and who should be involved. Although autonomy of the individual is important, those involved in the diagnostic process are encouraged to include family and other current or future caregivers during the disclosure process [412].

Specific guidelines for an optimal diagnostic disclosure process are hindered by the lack of systematic studies and inconsistency of desired approaches of patients and caregivers. Some caregivers want to be told directly and others would like a gentler explanation [420]. However, the disclosure process should be ongoing to ensure understanding of the diagnosis and any needed changes in the follow-up plans for the patient and family [412,421]. It has been shown that a contributor to the caregivers' dissatisfaction of the disclosure process is lack of follow-up appointments and limited information about community services [420].

To best provide diagnostic disclosure and appropriate connection to resources and services, providers need to consider the ability of the patient and caregiver to understand and cope with the diagnosis, the social and cultural context in which the patient lives [422], and whether the patient has a strong support network [421].

Providers sometimes tell patients about the diagnosis without using the words "Alzheimer's" or "dementia," perhaps in an attempt to soften the emotional impact of the diagnosis [376,396,407]. But such lack of clarity can lead to confusion for both patients and family members [403] and may endanger trust between patients and the medical team [407].

Using a standard approach for disclosing a diagnosis is not likely to be satisfactory because the same approach can be perceived by different patients and caregivers as either too blunt or too indirect [394,396,423]. Such difficulties have led to calls for the disclosure process to be managed in ways that are sensitive to each patient's and family's individual circumstances, using patient-centered approaches [394,412,421,423]. These approaches represent a distinct skill set, and providers

have recognized the need for training programs to help them improve their skills in this setting [405,406]. Efforts to improve how health care providers diagnose and manage Alzheimer's disease and dementia include educational components designed to improve the disclosure process [404,412,418].

7.7. Conclusion

Despite widespread recognition of the benefits of clear and accurate disclosure, the practices of health care providers vary widely. In several studies, including the current analysis of Medicare records, fewer than half of patients with a diagnosis of Alzheimer's or another dementia reported being told the diagnosis by their health care provider. Although caregivers were more likely to report disclosure, more than 45 percent did not report disclosure. Because of the complexity of the diagnostic and disclosure processes, varying preferences of patients and caregivers, and different support networks and coping mechanisms among patients, it is recognized that the disclosure process should be managed in a way that respects each patient's situation and that of their families and caregivers. Furthermore, health care providers have recognized the need for stronger support systems for themselves and for patients newly diagnosed with Alzheimer's disease or another dementia. Improvements in such systems have the potential to improve the care of individual patients and reduce the burden of disease on both caregivers and health care providers.

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End Notes

^{A1}*Number of Americans age 65 and older with Alzheimer's disease for 2015 (prevalence of Alzheimer's in 2015):* The number 5.1 million is from published prevalence estimates based on incidence data from the Chicago Health and Aging Project (CHAP) and population estimates from the 2010 U.S. Census [120].

^{A2}*Proportion of Americans age 65 and older with Alzheimer's disease:* The 11 percent is calculated by dividing the estimated number of people age 65 and older with Alzheimer's disease (5.1 million) by the U.S. population age 65 and older in 2015, as projected by the U.S. Census Bureau (47.7 million) = 11 percent. Eleven percent is the same as one in nine. (see 2012 National Population Projections: Summary Tables located at <http://www.census.gov/population/projections/data/national/2012/summarytables.html>).

^{A3}*Percentage of total Alzheimer's disease cases by age groups:* Percentages for each age group are based on the estimated 200,000 under 65, plus the estimated numbers (in millions) for people 65 to 74 (0.8), 75 to 84 (2.3), and 85+ (2.0) based on prevalence estimates for each age group and incidence data from the Chicago Health and Aging Project (CHAP) [120].

^{A4}*Differences between CHAP and ADAMS estimates for Alzheimer's disease prevalence:* The Aging, Demographics, and Memory Study (ADAMS) estimates the prevalence of Alzheimer's disease to be lower than does the Chicago Health and Aging Project (CHAP), at 2.3 million Americans age 71 and older in 2002 [122]. (Note that the CHAP estimates referred to in this end note are from an earlier study using 2000 U.S. Census data [168].) At a 2009 conference convened by the National Institute on Aging and the Alzheimer's Association, researchers determined that this discrepancy was mainly due to two differences in diagnostic criteria: (1) a diagnosis of dementia in ADAMS required impairments in daily functioning and (2) people determined to have vascular dementia in ADAMS were not also counted as having Alzheimer's, even if they exhibited clinical symptoms of Alzheimer's [123]. Because the more stringent threshold for dementia in ADAMS may miss people with mild Alzheimer's disease and because clinical-pathologic studies have shown that mixed dementia due to both Alzheimer's and vascular pathology in the brain is very common [6], the Association believes that the larger CHAP estimates may be a more relevant estimate of the burden of Alzheimer's disease in the United States.

^{A5}*Number of women and men age 65 and older with Alzheimer's disease in the United States:* The estimates for the number of U.S. women (3.2 million) and men (1.9 million) age 65 and older with Alzheimer's in 2013 is from unpublished data from the Chicago Health and Aging Project (CHAP). For analytic methods, see Hebert et al. [120].

^{A6}*Prevalence of Alzheimer's disease and other dementias in older whites, African-Americans and Hispanics:* The statement that African-Americans are twice as likely and Hispanics one and one-half times as likely as whites to have Alzheimer's disease and other dementias is the conclusion of an expert review of a number of multiracial and multi-ethnic data sources, as reported in detail in the Special Report of the Alzheimer's Association's 2010 *Alzheimer's disease Facts and Figures*.

^{A7}*State-by-state prevalence of Alzheimer's disease:* These state-by-state prevalence numbers are based on an analysis of incidence data from the Chicago Health and Aging Project (CHAP), projected to each state's population, with adjustments for state-specific age, gender, years of education, race and mortality [154]. Specific prevalence numbers projected for each year from 2015 to 2025 derived from this analysis were provided to the Alzheimer's Association by a team led by Liesi Hebert, Sc.D., Rush University Institute on Healthy Aging.

^{A8}*Number of new cases of Alzheimer's disease this year (incidence of Alzheimer's in 2015):* The East Boston Established Populations for Epidemiologic Study of the Elderly (EPESE) estimated that there would be 454,000 new cases in 2010 and 491,000 new cases in 2020. See Hebert et al. [155] The Alzheimer's Association calculated that the incidence of new cases in 2015 would be 461,400 by multiplying the 10-year change from 454,000 to 491,000 (37,000) by 0.5 (for the number of years from 2010 to 2015 divided by the number of years from 2010 to 2020), adding that result (18,500) to the Hebert et al. estimate for 2010 (454,000) = 472,500 [155]. Rounded to the nearest thousand, this is 473,000 new cases of Alzheimer's disease in 2015. The same technique for linear interpolation from 2000 to 2010 projections was used to calculate the number of new cases in 2015 for ages 65–74, 75–84, and 85 and older. The age group-specific Alzheimer's disease incident rate is the number of new people with Alzheimer's per population at risk (the total number of people in the age group in question). These incidence rates are expressed as number of new cases per 1000 people. Hebert et al. used the 2015 projected population generated from the 2000 U.S. Census to estimate age-specific rates, and these calculations depended on a particular 5-year age structure of the older adult population (e.g., percentage age 65–69, 70–74, etc.). To maintain compatibility with these calculations, we used the total number of people per age group (e.g., 65–74, 75–84, 85+) for 2015 from population projections from the 2000 U.S. Census (see 2000 National Population Projections: Summary Tables located at <http://www.census.gov/population/projections/files/natproj/summary/np-t3-d.pdf>).

^{A9}*Number of seconds for the development of a new case of Alzheimer's disease:* Although Alzheimer's does not present suddenly like stroke or heart attack, the rate at which new cases occur can be computed in a similar way. The 67 seconds number is calculated by dividing the number of seconds in a year (31,536,000) by the number of new cases in a

year.^{A8} The number of seconds in a year (31,536,000) divided by 472,500 = 66.7 seconds, rounded to 67 seconds. Using the same method of calculation for 2050, 31,536,000 divided by 959,000 (from Hebert et al. [155]) = 32.8 seconds, rounded to 33 seconds.

^{A10}*Criteria for identifying subjects with Alzheimer's disease and other dementias in the Framingham Study:* Starting in 1975, nearly 2800 people from the Framingham Study who were age 65 and free of dementia were followed for up to 29 years. Standard diagnostic criteria (DSM-IV criteria) were used to diagnose dementia in the Framingham Study, but, in addition, the subjects had to have at least "moderate" dementia according to the Framingham Study criteria, which is equivalent to a score of 1 or more on the Clinical Dementia Rating (CDR) Scale, and they had to have symptoms for six months or more. Standard diagnostic criteria (the NINCDS-ADRDA criteria from 1984) were used to diagnose Alzheimer's disease. The examination for dementia and Alzheimer's disease is described in detail in Seshadri et al. [130] The definition of Alzheimer's disease and other dementias used in the Framingham Study was thus very strict; using a definition that includes milder disease and disease of less than six months' duration, lifetime risks of Alzheimer's disease and other dementias would be much higher than those estimated by this study.

^{A11}*Projected number of people with Alzheimer's disease:* This comes from the CHAP study [120]. Other projections are somewhat lower (see, for example, Brookmeyer et al. [S1]) because they relied on more conservative methods for counting people who currently have Alzheimer's disease.^{A8} Nonetheless, these estimates are statistically consistent with each other, and all projections suggest substantial growth in the number of people with Alzheimer's disease over the coming decades.

^{A12}*Projected number of people age 65 and older with Alzheimer's disease in 2025:* The number 7.1 million is based on a linear extrapolation from the projections of prevalence of Alzheimer's for the years 2020 (5.8 million) and 2030 (8.4 million) from CHAP [120].

^{A13}*Previous high and low projections of Alzheimer's disease prevalence in 2050:* High and low prevalence projections for 2050 from the U.S. Census were not available for the most recent analysis of CHAP data [120]. The previous high and low projections indicate that the projected number of Americans with Alzheimer's in 2050 age 65 and older will range from 11 to 16 million [168].

^{A14}*Annual mortality rate due to Alzheimer's disease by state:* Unadjusted death rates are presented rather than age-adjusted death rates in order to provide a clearer depiction of the true burden of mortality for each state. States such as Florida with larger populations of older people will have a larger burden of mortality due to Alzheimer's.

^{A15}*Number of family and other unpaid caregivers of people with Alzheimer's and other dementias:* To calculate this number, the Alzheimer's Association started with data from the Behavioral Risk Factor Surveillance System

(BRFSS). In 2009, the BRFSS survey asked respondents age 18 and over whether they had provided any regular care or assistance during the past month to a family member or friend who had a health problem, long-term illness or disability. To determine the number of family and other unpaid caregivers nationally and by state, we applied the proportion of caregivers nationally and for each state from the 2009 BRFSS (as provided by the Centers for Disease Control and Prevention, Healthy Aging Program, unpublished data) to the number of people age 18 and older nationally and in each state from the U.S. Census Bureau report for July 2014. Available at: www.census.gov/popest/data/datasets.html. Accessed on Jan. 3, 2015. To calculate the proportion of family and other unpaid caregivers who provide care for a person with Alzheimer's or another dementia, the Alzheimer's Association used data from the results of a national telephone survey conducted in 2009 for the National Alliance for Caregiving (NAC)/AARP [S2]. The NAC/AARP survey asked respondents age 18 and over whether they were providing unpaid care for a relative or friend age 18 or older or had provided such care during the past 12 months. Respondents who answered affirmatively were then asked about the health problems of the person for whom they provided care. In response, 26 percent of caregivers said that: (1) Alzheimer's or another dementia was the main problem of the person for whom they provided care, or (2) the person had Alzheimer's or other mental confusion in addition to his or her main problem. The 26 percent figure was applied to the total number of caregivers nationally and in each state, resulting in a total of 15,705,824 Alzheimer's and dementia caregivers.

^{A16}*The 2014 Alzheimer's Association Women and Alzheimer's Poll* questioned a nationally-representative sample of 3102 American adults about their attitudes, knowledge and experiences related to Alzheimer's disease and dementia from January 9, 2014, to January 29, 2014. An additional 512 respondents who provided unpaid help to a relative or friend with Alzheimer's disease or a related dementia were asked questions about their care provision. Random selections of telephone numbers from landline and cell phone exchanges throughout the United States were conducted. One individual per household was selected from the landline sample, and cell phone respondents were selected if they were 18 years old or older. Interviews were administered in English and Spanish. The poll "oversampled" Hispanics, selected from U.S. Census tracts with higher than an 8 percent concentration of this group. A list sample of Asian Americans was also utilized to oversample this group. A general population weight was used to adjust for number of adults in the household and telephone usage; the second stage of this weight balanced the sample to estimated U.S. population characteristics. A weight for the caregiver sample accounted for the increased likelihood of female and white respondents in the caregiver sample. Sampling weights were also created to account for the use of

two supplemental list samples. The resulting interviews comprise a probability-based, nationally representative sample of U.S. adults. A caregiver was defined as an adult over age 18 who, in the past 12 months, provided unpaid care to a relative or friend age 50 or older with Alzheimer's or another dementia. Questionnaire design and interviewing were conducted by Abt SRBI of New York.

^{A17}*Number of hours of unpaid care:* To calculate this number, the Alzheimer's Association used data from a follow-up analysis of results from the 2009 NAC/AARP national telephone survey (data provided under contract by Matthew Greenwald and Associates, Nov. 11, 2009). These data show that caregivers of people with Alzheimer's and other dementias provided an average of 21.9 hours a week of care, or 1139 hours per year. The number of family and other unpaid caregivers (15,705,824)^{A15} was multiplied by the average hours of care per year, which totals 17.886 billion hours of care.

^{A18}*Value of unpaid caregiving:* To calculate this number, the Alzheimer's Association used the method of Amo et al. [S3]. This method uses the average of the federal minimum hourly wage (\$7.25 in 2014) and the mean hourly wage of home health aides (\$17.09 in July 2014) [S4]. The average is \$12.17, which was multiplied by the number of hours of unpaid care (17.886 billion) to derive the total value of unpaid care (\$217.67 billion).

^{A19}*Higher health care costs of Alzheimer's caregivers:* This figure is based on a methodology originally developed by Brent Fulton, Ph.D., for *The Shriver Report: A Woman's Nation Takes on Alzheimer's*. A survey of 17,000 employees of a multinational firm based in the United States estimated that caregivers' health care costs were 8 percent higher than non-caregivers' [S5]. To determine the dollar amount represented by that 8 percent figure nationally and in each state, the 8 percent figure and the proportion of caregivers from the 2009 Behavioral Risk Factor Surveillance System^{A15} were used to weight each state's caregiver and non-caregiver per capita personal health care spending in 2009 [S6], inflated to 2014 dollars. The dollar amount difference between the weighted per capita personal health care spending of caregivers and non-caregivers in each state (reflecting the 8 percent higher costs for caregivers) produced the average additional health care costs for caregivers in each state. Nationally, this translated into an average of \$639. The amount of the additional cost in each state, which varied by state from a low of \$471 in Utah to a high of \$974 in the District of Columbia, was multiplied by the total number of unpaid Alzheimer's and dementia caregivers in that state^{A15} to arrive at that state's total additional health care costs of Alzheimer's and other dementia caregivers as a result of being a caregiver. The combined total for all states was \$9.773 billion. Fulton concluded that this is "likely to be a conservative estimate because caregiving for people with Alzheimer's is more stressful than caregiving for most people who don't have the disease" [S7].

^{A20}*Lewin Model on Alzheimer's and dementia costs:* These numbers come from a model created for the Alzheimer's Association by The Lewin Group and adopted in January 2015. The model estimates total payments for health care, long-term care and hospice for people with Alzheimer's disease and other dementias based on cost data from the 2008 Medicare Current Beneficiary Survey. A comprehensive report on the model, *Changing the Trajectory of Alzheimer's disease: How a Treatment by 2025 Saves Lives and Dollars*, was published by the Alzheimer's Association in February 2015. The report and additional information on the model, its long-term projections and its methodology are available at alz.org/trajectory.

^{A21}*All cost estimates were inflated to year 2014 dollars using the Consumer Price Index (CPI):* All cost estimates were inflated using the seasonally adjusted average prices for medical care services from all urban consumers. The relevant item within medical care services was used for each cost element. For example, the medical care item within the CPI was used to inflate total health care payments; the hospital services item within the CPI was used to inflate hospital payments; and the nursing home and adult day services item within the CPI was used to inflate nursing home payments.

^{A22}*Medicare Current Beneficiary Survey Report:* These data come from an analysis of findings from the 2008 Medicare Current Beneficiary Survey (MCBS). The analysis was conducted for the Alzheimer's Association by Julie Bynum, M.D., M.P.H., Dartmouth Institute for Health Policy and Clinical Care, Center for Health Policy Research [179]. The MCBS, a continuous survey of a nationally representative sample of about 16,000 Medicare beneficiaries, is linked to Medicare Part B claims. The survey is supported by the U.S. Centers for Medicare and Medicaid Services (CMS). For community-dwelling survey participants, MCBS interviews are conducted in person three times a year with the Medicare beneficiary or a proxy respondent if the beneficiary is not able to respond. For survey participants who are living in a nursing home or another residential care facility, such as an assisted living residence, retirement home or a long-term care unit in a hospital or mental health facility, MCBS interviews are conducted with a nurse who is familiar with the survey participant and his or her medical record. Data from the MCBS analysis that are included in *2015 Alzheimer's disease Facts and Figures* pertain only to Medicare beneficiaries age 65 and older. For this MCBS analysis, people with dementia are defined as:

- Community-dwelling survey participants who answered yes to the MCBS question, "Has a doctor ever told you that you had Alzheimer's disease or dementia?" Proxy responses to this question were accepted.
- Survey participants who were living in a nursing home or other residential care facility and had a diagnosis of

Alzheimer's disease or dementia in their medical record.

- Survey participants who had at least one Medicare claim with a diagnostic code for Alzheimer's disease and other dementias in 2008. The claim could be for any Medicare service, including hospital, skilled nursing facility, outpatient medical care, home health care, hospice or physician, or other health care provider visit. The diagnostic codes used to identify survey participants with Alzheimer's disease and other dementias are 331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 331.82, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 291.2, 294.0, 294.1, 294.10 and 294.11.

Costs from the MCBS analysis are based on responses from 2008 and reported in 2014 dollars.

^{A23}*Differences in estimated costs reported by Hurd and colleagues:* Hurd et al. [196] estimated per-person costs using data from participants in ADAMS, a cohort in which all individuals underwent diagnostic assessments for dementia. *2015 Alzheimer's disease Facts and Figures* estimated per-person costs using data from the Medicare Current Beneficiary Survey (MCBS). One reason that the per-person costs estimated by Hurd et al. are lower than those reported in *Facts and Figures* is that Alzheimer's disease AMS, with its diagnostic evaluations of everyone in the study, is more likely than MCBS to have identified individuals with less severe or undiagnosed Alzheimer's. By contrast, the individuals with Alzheimer's registered by MCBS are likely to be those with more severe, and therefore more costly, illness. A second reason is that Hurd et al.'s estimated costs reflect an effort to isolate the incremental costs associated with Alzheimer's disease and other dementias (those costs attributed only to dementia), while the per-person costs in *2015 Alzheimer's disease Facts and Figures* incorporate all costs of caring for people with the disease (regardless of whether the expenditure was related to dementia or a coexisting condition).

^{A24}*The source for long-term care costs differs from the source used in prior years of this report:* Some long-term care costs for 2015 are lower than those reported in the *2014 Alzheimer's Disease Facts and Figures*. There are several possible explanations for these differences, including differences in the methodologies used, differ-

ences in the long-term care organizations included in each survey, or changes in the underlying cost structures.

^{A25}*Individuals with Medicare claims for more than one cancer type* were excluded from the analysis because the calculation algorithm did not support this situation.

^{A26}*Method of calculating the disclosure rate:* The number of respondents with a Medicare claim related to a specified medical condition and who responded "Yes" to the question of whether a doctor had that condition divided by the number of respondents with a Medicare claim related to that medical condition.

^{A27}*Disclosure rates are based on calculations incorporating data from the 2008, 2009 and 2010 Medicare Current Beneficiary Surveys and Medicare claims data:* Calculations and related analyses were performed under contract by Avalere Health, LLC.

^{A28}*Ninety-five percent confidence intervals for disclosure rates* did not overlap with the 95% confidence intervals for Alzheimer's disease or other dementias.

^{A29}*Comparisons were considered statistically significant* if the 95% confidence intervals did not overlap.

Supplementary References

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BAILES

EXHIBIT 17

Review

Clinical and genetic heterogeneity of amyotrophic lateral sclerosis

Sabatelli M, Conte A, Zollino M. Clinical and genetic heterogeneity of amyotrophic lateral sclerosis. Clin Genet 2013; 83: 408–416. © John Wiley & Sons A/S. Published by Blackwell Publishing Ltd, 2013

Although clinical picture of amyotrophic lateral sclerosis (ALS) is a stereotypical one, resulting from combination of signs secondary to dysfunction of both upper motor neuron (UMN) and lower motor neuron (LMN), clinical heterogeneity is a consistent feature of the disease. Age of onset, relative mix of UMN and LMN signs, duration of the disease and association with other conditions are major factors contributing to variable clinical phenotypes. Genetically, familial forms of ALS are associated with a large number of pleiotropic genes whose mutations impair different biochemical pathways, resulting in overlapping clinical and pathological phenotypes. Over the last few years contribution of large- and low-effect genes to sporadic ALS is increasingly recognized.

Conflict of interest

The authors report no conflicts of interest.

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Key words: amyotrophic lateral sclerosis – Mendelian genes – penetrance – phenotype – prognosis

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Amyotrophic lateral sclerosis (ALS) is characterized by relentless degeneration of upper motor neuron (UMN) and lower motor neuron (LMN) leading to progressive muscular paralysis. The disease occurs as sporadic amyotrophic lateral sclerosis (SALS) in the majority of cases, while nearly 5% of patients have a positive familial amyotrophic lateral sclerosis (FALS) (1). The question of whether ALS is a single disease with variable phenotypic expression or different diseases with heterogeneous causes has represented a matter of lively debate in the literature over the last few years (2). The discovery of mutations in *SOD1* as causative of FALS (3), in 1993, started the molecular genetics era of ALS research and over the last 20 years an increasing number of causative genes have been identified, revealing a high degree of genetic heterogeneity.

Clinical heterogeneity

Clinical picture of ALS is a stereotypical one, resulting from combination of signs secondary to dysfunction of both UMN and LMN (4). However, clinical heterogeneity is a recognized feature of the disease due to the following factors.

Age of onset

Mean age of disease onset is about 65 years in population-based studies (5). ALS affects people of all ages but the age-adjusted incidence rate varies greatly in different age groups. Incidence is very low in the first four decades (1.5/100,000/year), increases abruptly around age 40, reaching its peak between ages 60 and 79 (10–15/100,000/year), and decreases thereafter (5).

The presence of a peak in the age-specific incidence curve suggests that the disease results from a time-dependent exposure to some genetic or environmental risk factors. According to this hypothesis, early onset of the disease might reflect a major exposure to one or more of these risk factors (6). Interestingly, patients with young-onset ALS with onset in the third to fourth decade disclose peculiar clinical features, including predominant UMN signs, male prevalence, less common bulbar onset and more prolonged survival (6).

Juvenile ALS

In rare patients, labeled as juvenile amyotrophic lateral sclerosis (JALS), onset occurs in the first two decades. JALS is an heterogeneous condition distinct from

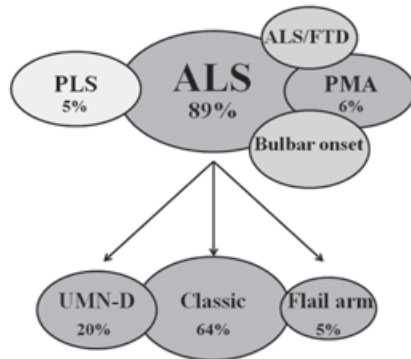


Fig. 1. Clinical phenotypes in our population of 850 patients with sporadic motor neuron disease. For legends see the text. Bulbar onset occurred in 28% of the group with amyotrophic lateral sclerosis–progressive muscular atrophy (ALS–PMA). Overt fronto-temporal dementia (FTD) affected 4.6% of patients.

classic ALS, as it usually has a relatively benign course and is familial in the great majority of cases (7, 8). However, an aggressive course may be observed in sporadic JALS and in some of these cases pathological examination showed peculiar cytoplasmic basophilic inclusions in motor neurons (9, 10).

Combination of UMN and LMN signs

The variable mix of UMN and LMN signs represents a major contributor to phenotypical heterogeneity of ALS (2, 4). Clinical manifestations of ALS exist on a continuum, ranging from apparently pure LMN dysfunction to severe pyramidal impairment with minor LMN signs. Classic ALS (Charcot type) is the most frequent form, accounting for about 70–90% of cases (Fig. 1). It is characterized by predominant LMN signs combined with slight to moderate pyramidal signs. Included in this category are also patients with preserved reflexes in atrophic limbs, or central conduction time prolongation at motor evoked potentials. In a minority of ALS patients clinical manifestations are dominated by pyramidal signs, consisting mainly of severe spino-bulbar spasticity, associated with slight LMN signs. This category, termed upper motor neuron-dominant (UMN-D) ALS, shows significant differences in age of onset, sex ratio, pattern of spreading and prognosis with respect to classic ALS, suggesting different disease mechanisms (11). Patients with pure LMN signs without any accompanying clinical or electrophysiological UMN signs are labeled as progressive muscular atrophy (PMA). However, it should be considered that pyramidal signs can be masked by LMN dysfunction at both clinical and electrophysiological level. This observation may explain the demonstration of UMN pathology in half of PMA patients at autopsy (12). The hypothesis that PMA and ALS are distinct entities is unlikely, as they show large clinical and genetic overlapping (13, 14).

About 2–5% of patients with motor neuron disease shows an exclusive involvement of UMNs with predominant spino-bulbar spasticity, and this condition has been labeled as primary lateral sclerosis (PLS) (15).

Clinical and genetic heterogeneity of ALS

Some evidences suggest that PLS is a distinct entity, including onset after 40 years, long disease duration and absence of familiarity. However, a small proportion of PLS patients develop LMN signs, usually within 3–4 years, making the separation from ALS problematical (16).

Site of onset

A consistent feature of ALS is that it starts as a focal process involving variable regions in the neuraxis and then spreads through all the motor system (17). On the basis of the clinical pattern in the initial phase of illness, different variants have been described, including bulbar, spinal and pseudoneuritic forms, flail arm syndrome, and Mill's hemiparetic type (2, 4). Body region onset may prove to be an important tool for assigning nosology. Consistently, the flail arm form is characterized by symmetric, predominantly proximal, wasting and weakness of both arms with relative sparing of lower limbs. This ALS form is prevalent in males, starts after the age of 40 and shows a slightly better clinical course with respect to classic ALS (18). Patients with bulbar onset ALS usually present with dysarthria and dysphagia, limbs symptoms can develop simultaneously with bulbar symptoms or can occur within 1–2 years. Bulbar onset ALS is more frequent in females and has a worse prognosis with respect to the spinal onset form. The term progressive bulbar palsy was historically used to designate this subset of ALS, but evidence that it represents a distinct entity is uncertain.

Survival

Median survival of ALS is approximately 3 years after the onset, but duration of the disease varies widely in individual patients, ranging from few months to over 10 years (6, 19). There is a general consensus in considering older age and bulbar onset as major negative prognostic factors (19). The UMN-D phenotype appears to be a strong independent predictor of long survival (6, 11). Disease duration depends on the timing of involvement of respiratory muscles. Of note, both temporal and spatial pattern of spreading of the disease process in different body regions are highly variable among patients. Respiratory weakness may represent the onset symptom in 5% of patients or can take place later in the course of the disease, as in flail arm ALS and in UMND forms (2, 11, 18).

Association with other conditions

ALS has been generally considered a paradigm of pure motor neuron disorder. Nevertheless, it is currently recognized that pathologic changes are not limited to motor systems. Patients with ALS may exhibit cognitive abnormalities ranging from impaired frontal executive dysfunction to overt fronto-temporal dementia (FTD) (20). A recent population-based study showed that

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comorbid dementia occurs in approximately 14% of patients with a new diagnosis of ALS (21). Cognitive impairment, predominantly in the form of executive dysfunction, occurs in more than 40% of ALS patients who have no evidence of dementia. Further support for the concept that FTD and ALS are closely related conditions is the recognition of families with pure FTD, pure ALS and ALS/FTD. Of note, both ALS and FTD show neuronal inclusions positive for the transactive response DNA-binding protein 43 TDP-43 (22) and share many gene defects, including *C9ORF72*, *TARDBP*, *FUS* (fused-in-sarcoma) and *VCP* mutations.

Association of ALS with Parkinson disease (PD) has been reported as well (23, 24). Supporting the link between ALS and PD is the identification of mutations in *TARDBP* (25), *ATXN2* (26, 27), *C9ORF72* (28, 29) and *ANG* (30) in both conditions.

Genetics of ALS

The Juvenile form of ALS is familial in the great majority of cases, with both autosomal-recessive and autosomal-dominant pattern of inheritance. Mutations in several genes, including *ALSIN*, *SETX*, *Spatacsin* and *SIGMAR1* have been shown as the underlying cause of the disease (31).

Regarding the classic adult-onset form, most cases occur as FALS, and only a small proportion of patients have a positive FALS, varying from 1% to 11.6% in large reported series. A recent meta-analysis of data showed that the rate of FALS among prospective population-based registries was 5.1% (1). ALS is considered to be familial if one or more relatives are reported as affected by the same disease, but the number of affected relatives and degree of relationship vary greatly among kindreds. Importantly, in 50–75% of FALS only two affected relatives are reported in families (32, 33). In these instances the pattern of inheritance is unclear and there is an uncertainty as to whether these patients should be classified as FALS (34). In fact, the possibility that a second person among relatives is affected by chance may not be excluded. Criteria were recently proposed for classifying FALS into possible, probable and definite groups (35). Genetic component due to the currently known ALS genes has been shown to vary greatly among these three categories of FALS (33).

Genetics of FALS

To date, a large number of genes causing or pre-disposing to ALS have been identified (<http://alsod.iop.kcl.ac.uk/>). Actually, only a limited number of genes, including *C9ORF72* (36, 37), *SOD1* (3), *TARDBP* (38, 39) and *FUS* (40, 41), are responsible for a considerable proportion of FALS cases. A constellation of other genes, each causing very few FALS cases, are increasingly recognized. This latter group includes *VAPB*, *FIG 4*, *CHMP2B*, *OPTN*, *DAO*, *VCP*, *UBQLN2* and *SQSTM1*. Mutations in *PFN1*, the most

recently discovered gene, are very rare (42). About 50–60% of FALS cases have mutations in these genes. (43–45).

C9ORF72

A large hexanucleotide (GGGGCC) repeat expansion in the first intron of *C9ORF72* located on chromosome 9p21 is the most common mutation detected in patients with familial ALS (36, 37, 43–49). Mutation frequency varies between different populations, countries and regions, ranging from 0% to 18% in Asiatic countries to 46% in Finland and France. The percentage of mutated cases raises to 50–72% in families with ALS/FTD phenotype (43, 46). Notably, mutations in *C9ORF72* are the most common cause of familial FTD as well, accounting for 11.7–17.8 of cases (36, 47, 48). The associated risk haplotype is shared by most ALS families of European ancestry, suggesting a common founder (37, 46).

The protein encoded by *C9ORF72* is unknown. Using fluorescence *in situ* hybridization technique with a probe targeting the GGGGCC repeat, multiple nuclear RNA foci of an abnormal mRNA have been detected in brain tissues from patients carrying the expanded repeat, suggesting a toxic gain-of-function mechanism. However, reduced expression of one of the transcripts of *C9ORF72* has been observed as well, consistent with a loss-of-function mechanism (36, 37). At a neuropathological level, patients with mutations in *C9ORF72* show TDP-43-immunoreactive protein aggregates, and presence of ubiquitin-positive, TDP-43-negative inclusions in a variety of neuroanatomical regions (49).

Comparing the phenotype with that of patients carrying mutations in other ALS-related genes and of patients with unidentified genetic defects, those with *C9ORF72* expansion show some consistent differences (28, 43–45, 49). The most notable one is a significantly higher frequency of cognitive impairment which affects 40–50% of cases compared with 8–9% of non-*C9ORF72* expansion cases. In patients carrying *C9ORF72* mutations bulbar onset seems more frequent and median survival consistently lower than in patients carrying *TARDBP*, *SOD1* or unknown mutations. *C9ORF72* expansion is more frequent among patients with onset >61 years (45).

SOD1

Mutations in *SOD1*, the superoxide dismutase 1 encoding gene, have been found in 12–23% of FALS (<http://alsod.iop.kcl.ac.uk/>). *SOD1* is a 153 amino acids protein which is expressed in all cells. Mechanisms by which mutated *SOD1* cause the disease remain enigmatic. It is currently considered that mutant *SOD1* causes neurodegeneration by an acquired novel cytotoxic activity which is multifactorial, affecting DNA/RNA metabolism, mitochondria, neurofilaments and axonal transport, function of the endoplasmic reticulum, the Golgi apparatus and the proteasome (50).

Clinical and genetic heterogeneity of ALS

One hundred sixty-six mutations have been identified so far throughout all five exons, consisting mostly of missense mutations, while non-sense mutations or gene deletions are uncommon. Most *SOD1* mutations are autosomal dominant, but the D90A variant can be transmitted in either a dominant or a recessive manner (51, 52). In patients with *SOD1* mutations cognitive impairment is very rare (0–2.6%) and bulbar onset is observed less frequently (7–12%) than in non-*SOD1* patients (44, 45, 53). Mean age of onset is greater than in *FUS* patients but it is lower than in other non-*SOD1* patients. Specific gene variants, including L106V, G37R and L38V, are associated with young onset (53).

Duration of the disease is quite heterogeneous, varying from few months to decades (44, 45, 53). Some mutations, including D90A, G37R, G41D, G93C and D11Y, have been consistently associated with prolonged survival while others, such as A4V and G85S, with aggressive course. Frequency of individual mutations varies in different countries. The A4V variant is the most frequent mutation in North America, occurring in about 50% of *SOD1* FALS cases, while it is relatively rare in Europe.

TARDBP and *FUS*

The identification of mutations in these two genes in cases of both familial and sporadic ALS was a major breakthrough in the history of ALS research as it represented the convergence of genetic research into earlier neuropathologic studies. In 1988, several studies had shown that motor neurons and glial cells from ALS patients contained abnormal proteinaceous accumulations labeled by antiubiquitin antibodies (54, 55). Content of these inclusions was initially unknown. After the discovery of mutations in *SOD1* associated to FALS, it was showed that inclusions were stained with antibodies to SOD1 in patients with mutated *SOD1* (56). However, SOD1 was not a component of the inclusions in sporadic ALS and in non-*SOD1* familial forms. A landmark was the discovery of TDP-43 as major component of the protein aggregates (22). Notably, all cases of ALS, including sporadic ALS, ALS with dementia and *SOD1*-negative FALS had neuronal and glial inclusions that were immunoreactive for both ubiquitin and TDP-43, indicating a central role of TDP-43 in disease pathogenesis (57). The absence of TDP-43 pathology in cases with *SOD1* mutations suggests that different mechanisms underlie motor neuron degeneration (58). TDP-43 discovery was followed by the identification of mutations in *TARDBP*, the TDP-43 encoding gene, in a subset of ALS patients (38, 39). Soon after, mutations in *FUS*, encoding a protein with several structural and functional similarities with TDP-43, were discovered in FALS and SALS patients (40, 41). Also patients with mutated *FUS* showed cytoplasmic mislocalization of the FUS protein. Whether FUS is involved in the pathogenesis of SALS and other forms of FALS without *FUS* mutations is currently controversial.

It was recently reported that FUS-immunoreactive inclusions are a common finding in sporadic and in non-*SOD1* familial ALS without *FUS* mutations (59).

TDP43 and FUS are DNA/RNA-binding proteins which are able to shuttle between nucleus and cytoplasm due to their content of a nuclear localization signal and a nuclear export signal (60). They play several functions related to RNA metabolism in both compartments, including transcription, splicing, transport, translation, degradation and microRNA processing. Both proteins are present predominantly in cell nuclei in physiological conditions. In ALS, mislocalization of FUS and TDP-43 in the cytoplasm with inclusion formation has been proposed to cause either a loss of the normal protein function in the nucleus, a gain of toxic function in the cytosol, or both (60).

TDP-43 is a 414 amino acid protein encoded by six exons and containing two RNA recognition motifs and a C-terminal glycine-rich region. Most of the identified mutations are localized in the glycine-rich region encoded by exon 6. Mutations in *TARDBP* have been identified in 2–5% of FALS (44, 45). Of note, a unique *TARDBP* missense mutation (p.A382T) has been found in approximately one third of all ALS cases in the island of Sardinia, a genetic isolate phylogenically distinct from other European populations (61). Regarding the clinical phenotype, cognitive impairment has been observed in 31% of patients with mutations in *TARDBP* (44). The rare occurrence of *TARDBP* mutations in patients with age of onset >61 years (45) has not been confirmed in other studies (62). Survival is longer than in *FUS* and *C9ORF72* mutated patients.

FUS is a 526 amino acid protein encoded by 15 exons. *FUS* mutations are found in 1–5% of FALS (40, 41, 44, 45). Most *FUS* mutations cluster in the C-terminus of the protein, encoded by exon 15, containing a non-classical nuclear localization sequence (40, 41). Impaired transportin-mediated nuclear import of FUS, resulting from disruption of this motif, has been shown as a mechanism for cytoplasmic mislocalization of FUS (63). Clinical phenotype of *FUS* mutated patients discloses some distinctive characteristics (44, 45, 64–67). Age of onset is consistently lower than in other FALS; *FUS* mutations are the most common genetic defect in FALS patients with the young onset form, affecting 35% of patients aged <40 years (45). Of importance, specific *FUS* mutations, including the missense variant P525L, frameshift mutations and gene deletions, have been identified in patients with juvenile onset (<25 years) and very aggressive course and in cases with basophilic inclusions (68–71). Predominant LMN signs, weakness of neck extensor muscles with proximal, nearly symmetric impairment of upper limb muscles are seen at onset in patients with the common R521C variant of *FUS* (64, 65). Cognitive impairment has been reported in 0–5% of FALS patients with *FUS* mutations. Survival is significantly shorter than in other FALS, with exceptional patients living more than 4 years.

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Genetics of sporadic ALS

There is increasing evidence that the dichotomy between familial and apparently sporadic ALS is artificial as genetic factors may play a relevant role also in the pathogenesis of SALS. From a clinical point of view patients with SALS are indistinguishable from those with FALS. Both conditions show similar pathological patterns, namely the presence of ubiquitinated TDP-43 positive inclusions. Heritability of apparently sporadic ALS has been addressed by examining the concordance among ALS patients and their relatives. On the basis of twin data studies, heritability of sporadic ALS was estimated to be 0.61 (0.38–0.78) (72). Other studies have shown a small but definite increased risk to first-degree relatives of patients with sporadic ALS (73).

High-penetrance susceptibility model

The observation that mutations in large-effect genes associated with FALS may be detected in cases with SALS is a major clue in favor of the genetic basis of SALS. In fact, discoveries of new genes involved in FALS have been invariably followed by the identification of mutations in the same genes in patients with apparently sporadic disease (Table 1). In a clinic based population about 11% of apparently sporadic ALS harbored mutation in major FALS genes (74). Considering that only 50–60% of patients with FALS have mutations in currently known genes, the discovery of new genes in the future is expected to increase the proportion of SALS with proven genetic etiology.

The detection of mutations in large-effect genes in ALS patients with no apparent family history may have several explanations. The first one is inaccuracy in the definition of FALS due to ascertainment bias. Lack of knowledge of family history, misdiagnosis of ALS in family members, early death due to other causes of family members prior to developing motor neuron degeneration are common sources of mistake. Furthermore, a large-effect gene mutation may not appear familial if the family size is small or if a single ALS gene predisposes to multiple neurodegenerative disorders. Indeed, pleiotropy seems to be a consistent feature of several genes, such as *C9ORF72*, *FUS*, *TARDBP*, *OPTN*, *FIG 4* and *ANG* (75). A second explanation for the occurrence of mutations in FALS genes in sporadic cases is that mutations may be *de novo* or low penetrant. *De novo FUS* mutations have been described in several cases of SALS disclosing early onset and aggressive course (10, 68, 70, 71). It is worth noting that *de novo* mutations are not reported in other genes with the exception of a single case of *SOD1* mutation (76). Supporting the hypothesis of incomplete penetrance is the frequent detection of the same mutations found in SALS patients also in unaffected relatives, including very old individuals (74).

Table 1. Proportion of sporadically amyotrophic lateral sclerosis (SALS) patients with mutated genes

Geographic origin	SOD1			TARDBP			FUS			C9ORF72		
	Geographic origin	% (N.)	Ref.	Geographic origin	% (N.)	Ref.	Geographic origin	% (N.)	Ref.	Geographic origin	% (N.)	Ref.
Italy	Italy	0.7% (303)	(85)	Italy	2.7% (480)	(74)	Italy	0.7% (964)	(86)	Italy	5.1% (1275)	(46)
Italy	Italy	2.1% (480)	(74)	Italy	1% (298)	(87)	Italy	0.6% (480)	(74)	Italy	3.7% (1624)	(88)
Italy	Italy	0% (225)	(89)	Italy	2.2% (541)	(62)	Italy	1.2% (327)	(90)	Italy–Sardinia	6.8% (133)	(88)
Italy	Italy	4.5% (66)	(91)	Italy–Sardinia	23.3% (104)	(61)	Italy	0.9% (436)	(92)	Greece	8.1% (136)	(93)
Spain	Spain	1.1% (87)	(94)	France	2.1% (285)	(95)	France–Quebec	0.7% (405)	(96)	France	8% (725)	(45)
Spain	Spain	4.2% (94)	(97)	France–Quebec	5% (120)	(39)	France–Quebec	1.1% (454)	(98)	Spain	3.2% (781)	(99)
Belgium	Belgium	1.4% (69)	(100)	Belgium	0% (237)	(101)	Germany	0.16% (596)	(102)	Germany	5.2% (421)	(103)
Scandinavia	Scandinavia	3.9% (355)	(104)	Finland	0% (44)	(105)	North England	0.2% (548)	(106)	Finland	21% (290)	(37)
Netherlands	Netherlands	0.4% (451)	(107)	Netherlands	0.4% (1192)	(78)	Netherlands	0.3% (1192)	(78)	Netherlands	6.1% (1422)	(108)
Scotland	Scotland	7% (57)	(109)	UK–Australia	0.5% (372)	(38)	USA	0.1% (1087)	(92)	Ireland	5% (386)	(28)
UK	UK	2.9% (175)	(110)	North America	0% (279)	(111)	Australia	0% (247)	(65)	England	6.8% (916)	(103)
UK	UK	2.6% (155)	(112)	China	0.96% (312)	(113)	China	0.9% (210)	(114)	USA	5.5% (1014)	(103)
Iran	Iran	4.2% (47)	(115)	China	0.6% (165)	(116)	China	0% (99)	(71)	Australia	5.3% (263)	(103)
Canada	Canada	1.9% (159)	(117)	Japan	0% (220)	(118)	Canada	0.6% (168)	(119)	Japan	0.4% (552)	(120)
Korea	Korea	1.2% (249)	(121)	Korea	0% (249)	(121)	Korea	1.6% (249)	(121)	Korea	0% (246)	(122)

Clinical and genetic heterogeneity of ALS

Oligogenic model

Patients harboring double mutations in ALS-associated genes are increasingly recognized (74, 77, 78). Evidence for a digenic inheritance in ALS is supported by two studies showing that the frequency of double mutations in both FALS and SALS is higher than that expected on the basis of chance (74, 78).

Low-penetrance susceptibility model

A different model might explain the genetic contribution to SALS. In a polygenic threshold model, SALS might result from summatory effects of a series of low frequency, weakly deleterious mutations in a variety of genes, each conferring a moderate increase in relative risk (79). According to this model, disease develops only once a critical threshold of liability is crossed, due to the cumulative contribution of multiple genetic and environmental factors. Several genes have been proposed but for most of them the role in the etiopathogenesis of SALS remains unclear (reviewed in Ref. (75, 80).

The predisposing role to SALS of CAG expansion in *ATXN2* has been consistently suggested by several association studies carried out on large series of patients and controls (26, 81, 82). The normal-size range of the *ATXN2* polyglutamine tract extends between 14 and 31 repeats, being 22 or 23 the most frequent ones. Expansions of more than 34 repeats are known to cause spinocerebellar ataxia type 2. Intermediate length of a 27–33 CAG repeat in *ATXN2* confers an increased risk for developing ALS. The association is mainly driven by the longer (31–33) polyQ repeats, which have been found in 1.8–3.7% of different series of patients, compared with 0–0.2% of control individuals. Supporting the pathogenic role of *ATXN2* is the observation that it is a modifier of TDP-43 and FUS toxicity (81, 83).

ANG was initially considered a Mendelian gene implicated in both FALS and SALS (84). In a recent analysis mutations in *ANG* were found in 0.46% of 6471 ALS patients, compared with 0.04% of 7668 control individuals (30). Although the frequency of *ANG* variants is very low, robust data indicate that *ANG* should be regarded as low-penetrance susceptibility gene for ALS.

Conclusions

There is increasing evidence that the level of clinical and etiological heterogeneity of ALS is far greater than previously assumed. Several clinical phenotypes of ALS may be identified, but no clear boundaries are observed among them, as they represent points on a spectrum. FALS is caused by several pleiotropic genes whose mutations impair different biochemical pathways, resulting in overlapping clinical and pathological phenotypes. A proven genetic etiology affects a considerable proportion of apparently SALS patients, with relevant implications in clinical practice and in a

research setting. Future studies will elucidate genetic component of SALS, including factors influencing penetrance.

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BAILES

EXHIBIT 18

RESEARCH ARTICLE

Chronic Traumatic Encephalopathy in Contact Sports: A Systematic Review of All Reported Pathological Cases

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with head trauma. Although initially believed to affect only boxers, the at-risk population has expanded to encompass a much wider demographic, including American football players, hockey players, wrestlers, and military veterans. This expansion has garnered considerable media attention and public concern for the potential neurodegenerative effects of head trauma. The main aim of this systematic review is to give a complete overview of the common findings and risk factors for CTE as well as the status quo regarding the incidence and prevalence of CTE. This systematic review was performed using PubMed and MEDLINE and includes all neuropathologically confirmed cases of CTE in the medical literature to date, from the first published case in 1954 to August 1, 2013 ($n = 153$). The demographics, including the primary source of mTBI (mild Traumatic Brain Injury), age and cause of death, ApoE genotype, and history of substance abuse, when listed, were obtained from each case report. The demographics of American football players found to have CTE are also presented separately in order to highlight the most prevalent group of CTE cases reported in recent years. These 153 case reports of CTE represent the largest collection to date. We found that a history of mTBI was the only risk factor consistently associated with CTE. In addition, we found no relationships between CTE and age of death or abnormal ApoE allele. Suicide and the presence of premorbid dementia was not strongly associated with CTE. We conclude that the incidence of CTE remains unknown due to the lack of large, longitudinal studies. Furthermore, the neuropathological and clinical findings related to CTE overlap with many common neurodegenerative diseases. Our review reveals significant limitations of the current CTE case reporting and questions the widespread existence of CTE in contact sports.

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Introduction

The damaging neurological effects of sports-related repetitive head trauma were described by Harrison S. Martland in 1928 [1]. His clinical description of ‘punch drunk syndrome’ in a group of former boxers has been extended to include a complex neuropathological and clinical

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diagnosis known today as Chronic Traumatic Encephalopathy (CTE). More recently case reports demonstrate pathologically confirmed CTE in former combat military personnel and contact sport athletes other than boxers. This has prompted renewed interest and controversy regarding the potential for long-term neurodegenerative changes to occur after concussive and even sub-concussive repetitive or blast wave associated head trauma [2, 3].

Thus far CTE research has been limited to selective case reports. There are no published systematic studies incorporating both sport and non-sport related head trauma populations. Based on this lack of data, it is currently impossible to determine the incidence of new cases occurring within contact sport. Additionally, overall prevalence of CTE amongst all cases of head trauma cannot be determined at this time. Finally, due to the fragmented data collected in case reports, no conclusions can be drawn about potential risk factors for developing CTE in contact sports [4]. To date, all pathologically confirmed CTE cases have had a history of head trauma; however, the reported degree of severity, frequency of blows to the head, and documentation of prior concussion is highly variable [5].

Several recent reviews have focused on the various neuropathological findings and the clinical criteria used for the diagnosis of CTE and have drawn attention to the confusion and inconsistency of the diagnosis of CTE [6–7]. These reviews have highlighted confounding neuropathological findings such as the presence of co-occurring neurodegenerative conditions including Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis (ALS) discovered at the time of death in those reported to have CTE.

In this review, we summarize all currently known cases of pathologically-confirmed CTE, from the first published case in 1954 to August 1, 2013. Our purpose is to provide a data-driven overview of all CTE cases to date. The demographics, including the primary source of mTBI (mild Traumatic Brain Injury), age and cause of death, ApoE genotype, and history of substance abuse, when listed, were obtained from each case report. The demographics of American football players found to have CTE are also presented separately in order to highlight the most prevalent group of the many CTE cases reported in recent years. Through this review we will describe the limitations of current CTE case reporting in order to place into context the lack of evidence for the widespread existence of CTE in contact sports.

Methods

We reviewed all known cases of pathologically confirmed CTE from the first published case in 1954 to August 1, 2013 using the online databases of PubMed, MEDLINE, and Google Scholar. Non-English language articles were included and translated. Initially, articles were identified using a combination of the following search terms: "chronic traumatic encephalopathy", "dementia pugilistica", "traumatic brain injury", "repetitive mTBI", "sports-related concussion", "neurodegenerative disease", "hyperphosphorylated tau", "tauopathy", "TDP-43 proteinopathy", "professional football", "boxing", "military veterans". Based on the abstracts, all studies that described neuropathological reports of CTE and DP were selected for review. In addition, all references from the selected articles were searched and any relevant references were also included in the review. Information from media reports was also screened for confirmed CTE cases. The subjects compiled in this review consist of pathologically confirmed cases of DP/CTE reported in the medical literature, and four subjects whose information was gathered from confirmed media reports. Exclusion criteria included: only presenting clinical findings of suspected head trauma-related neurodegeneration without post-mortem neuropathological confirmation, subjects not explicitly diagnosed with either DP or CTE, and duplicate cases republished in the medical literature, which were identified either by explicit flagging of the authors or by matching demographic information from previous studies by the same author.

Measures

Individuals were categorized according to the most likely source of potential head impact. Categories were: Boxer (amateur or professional), American football player (national football league (NFL), Canadian football league (CFL), semi-professional (semi-pro), collegiate football (collegiate), and high school (HS), ice hockey player (amateur or professional), wrestler (amateur or professional), military veteran or miscellaneous. If an athlete was also a military veteran, they were still categorized according to their sport involvement. Additional potential causes of head trauma, such as motor vehicle accident (MVA) and fights were also included when reported.

Age at death was included and classified according to a range over 10 years (i.e. 10–19, 20–29, etc.). Specific cause of death was also reported when available and was additionally classified as natural, accidental, or suicide.

Apolipoprotein (ApoE) genotype profiling was included if the original source provided the information. History of substance abuse was dichotomized (yes; no/unknown) based on information deducted from case reports and media reports, using substance abuse criteria from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [8] as guideline. Hence, individuals identified as having a positive history of substance abuse were not necessarily clinically diagnosed.

Results

A literature review of 180 sources rendered 40 articles reporting on one or more neuropathologically confirmed cases of CTE [2,3,5,9–45] (Fig 1). This review revealed a total of 262 confirmed cases of CTE. Of these 262 cases, 113 were determined to be duplicates, resulting in a total of 149 unique cases with pathologically confirmed CTE in the medical literature. In addition to these 149 cases, an additional 4 cases of CTE were identified in published media reports that were not also included in articles of the literature review [46–49]. A final cohort of 153 unique pathologically confirmed cases of CTE/DP was determined from combined literature and media reports data.

The 153 cases of CTE (S1 Table) included $n = 69$ (45.1%) former boxers, $n = 63$ (41.2%) former amateur and professional football players, $n = 5$ (3.3%) former hockey players, $n = 6$ (3.9%) former military veterans, $n = 3$ (2.0%) former professional wrestlers, and $n = 7$ (4.6%) miscellaneous cases [30–61]. Some of the former athletes are also military veterans ($n = 15$ former football players, $n = 11$ former boxers, and $n = 1$ former hockey player). With one exception, all diagnosed cases with CTE have been males.

The age of death was available for 150 cases and ranged from 17 to 98 years. Individuals 60–69 years of age made up the largest age demographic in this series (Table 1). Information about the cause of death was available for 111 cases. There were 78 deaths from natural causes; 19 accidental deaths, and 14 suicides. Common causes of natural death were respiratory failure, cardiac disease, failure to thrive associated with end-stage dementia, and malignancy. Common causes of accidental death were drug overdose and severe TBI injury.

ApoE allele genotyping data was available for 80 cases (Table 2). Of these, homozygous ApoE3 ($n = 49$; 61.3%) and heterozygous ApoE3/E4 ($n = 20$; 25%) were the most prevalent genotypes. Other genotypes such as Apo E2/E3 ($n = 4$; 5.1%), E2/E4 ($n = 2$; 2.5%), and E4/E4 ($n = 5$; 6.3%) were observed at much smaller frequencies.

Thirty (19.6%) cases had a documented history of substance abuse prior to or co-morbid with symptomatic CTE presentation (Tables 3, 4). Substances abused included alcohol, prescription painkillers, anabolic steroids, cocaine, methamphetamine, and marijuana.

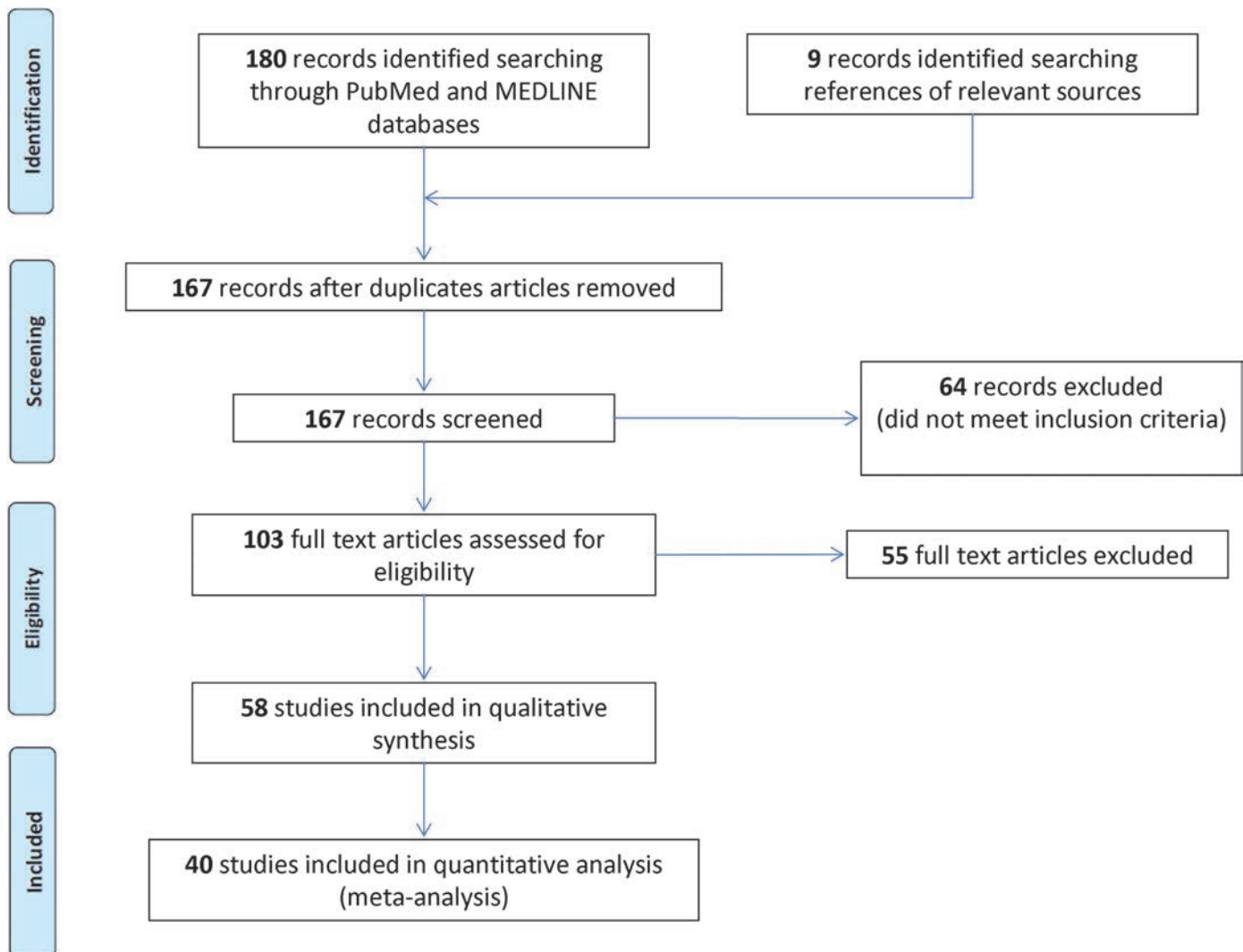


Fig 1. Prisma flowchart illustrating the number of included and excluded studies in the systematic review on Chronic Traumatic Encephalopathy in Contact Sports.

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There are inherent limitations on the numbers reported for substance abuse. The information gathered commenting on substance abuse was often a result of post mortem interviews from next of kin members who were likely unaware of the extent of abuse. Also substance abuse problems are difficult to diagnose and may go undetected by family members. Also, not able to gather information regarding the extent and frequency of substance abuse.

Since 2002, the majority of CTE cases documented in the literature have involved American football players. Now totaling 63 subjects, football players are second only to boxers in terms of documented CTE diagnoses in the medical literature. Of the 63 former football players, 6 played only high school level and 9 through the collegiate level. At the professional level, 42 played in the National Football League (NFL), 4 the Canadian Football League (CFL), and 1 played semi-professional football. Age of death was available for all 63 players, with the most common age range of death being 60–69 years (Table 1). Cause of death was also available for all 63 football player, with $n = 41$ dying from natural causes (65.1%), $n = 11$ from accidental causes (17.5%), and $n = 11$ from suicide (17.5%). ApoE allele genotyping data was available for

Table 1. Age group distribution in CTE diagnosed subjects.

Age range	Overall cases n (%)		Football cases n (%)	
10–19	3	(2.0%)	3	(4.8%)
20–29	16	(10.7%)	5	(7.9%)
30–39	9	(6.0%)	6	(9.5%)
40–49	21	(14.0%)	11	(17.5%)
50–59	21	(14.0%)	6	(9.5%)
60–69	39	(26.0%)	13	(20.6%)
70–79	26	(17.3%)	10	(15.9%)
80–89	12	(8.0%)	8	(12.7%)
90–99	3	(2.0%)	1	(1.6%)
Total	150		63	

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53 out of 63 of the football players (84.1%; [Table 2](#)). A positive history of substance abuse was found in 9 football players (14.3%; [Table 4](#)).

Discussion

This review of 153 pathologically confirmed cases of CTE represents the most current and most complete number of confirmed CTE cases in the medical literature. The final number of CTE cases was determined after accounting for 113 duplicate reported cases. Duplicate cases accounted for 43% of all cases of CTE identified in the medical literature by this review. Although the authors of this review acknowledge the occasional need for re-evaluating former CTE cases in order to further understand CTE findings presented to date, the high rate of re-reporting cases often without explicit notation of previous documentation has led to an erroneous, inflated impression of the number of CTE cases reported. The 153 CTE cases described in this review also include four unique cases of CTE found in media reports which were substantiated by cross confirmation from multiple sources including quotes from CTE investigators [46–49].

Of the 153 unique pathologically confirmed cases of CTE, six major mTBI subgroups were identified: former boxers, former football players, former hockey players, former military veterans, former professional wrestlers, and other miscellaneous causes of head trauma. Former boxers and football players made up the majority of all cases (86.2%). This observation is consistent with the long standing history of CTE research in the sport of boxing and the recent focus on former football players.

Starting in 1954 the pathological diagnosis of CTE, first recognized in a former boxer, remained exclusive to this sport for 35 years until it was observed in a non-boxing subject in 1989 [11,40]. The modern interest in CTE began in 2002 with the seminal diagnosis of CTE in a former professional football player by Dr. Bennett Omalu [35]. Since then, football has been the most studied mTBI subgroup for CTE accounting for 63 cases compared to boxing's 17 during the same time period. The remaining mTBI subgroups identified since 2002, including former combat military personnel and other contact sport athletes such as ice hockey players, have yet to be studied to the same extent as either boxers or football players. This is also true for athletes of contact sports with risk for head impact but with no confirmed CTE cases to date, such as rugby or soccer players. Based on the current state of CTE research, we have no reason to hypothesize that the clinical and pathological presentation of CTE in other contact

Table 2. ApoE genotype breakdown in CTE diagnosed subjects.

ApoE genotype	Overall cases n (%)		Football cases n (%)		% of normal population
$\epsilon 3/\epsilon 3$	49	(62.0%)	32	(60.4%)	58.5%
$\epsilon 2/\epsilon 3$	4	(5.1%)	4	(7.5%)	13.6%
$\epsilon 2/\epsilon 2$	0	(0.0%)	0	(0.0%)	0.3%
$\epsilon 2/\epsilon 4$	2	(2.5%)	1	(1.9%)	2.4%
$\epsilon 3/\epsilon 4$	20	(25.3%)	11	(20.8%)	22.2%
$\epsilon 4/\epsilon 4$	5	(6.3%)	5	(9.4%)	2.9%
Total	80		53		

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sports would systematically differ from the CTE presentation in boxers or football players; yet, more systematic research data is necessary to evaluate this hypothesis.

Despite media speculation and several prominent CTE research groups purporting to estimate the prevalence of CTE in former boxers and football players, there has not yet been a large, longitudinal study conducted to substantiate any estimates [50,51]. The number of former participants in contact sports and military combat with a reported history of mTBI is estimated to be in the millions and to determine the actual incidence and prevalence of CTE would require thousands of participants and would need to span decades. The 4th International Conference on Concussion in Sport in 2012 also concluded the prevalence and causation of CTE cannot be inferred at this time [4] (see Consensus Statement below).

2012 Consensus Statement on Concussion in Sport: *Chronic traumatic encephalopathy*

“Clinicians need to be mindful of the potential for long-term problems in the management of all athletes. However, it was agreed that chronic traumatic encephalopathy (CTE) represents a distinct tauopathy with an unknown incidence in athletic populations. It was further agreed that a cause and effect relationship has not as yet been demonstrated between CTE and concussions or exposure to contact sports. At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. It was also recognized that it is important to address the fears of parents/athletes from media pressure related to the possibility of CTE [4].”

Cause and age of death. The age of death reported in 150 CTE cases ranged from 17 to 98 years old, with the median age of death falling in the range of 60 to 69 years. This represents an earlier average age of death compared to the general US male population age of death of 76.2 years [52]. Of the CTE cases, 72.7% died before the age of 70. Of the 111 CTE cases that included cause of death, none listed CTE as cause of death. The majority of the CTE subjects died

Table 3. History of substance (ab)use in CTE diagnosed subjects.

Substances (ab)used	Number of cases	% of all substances abuse
Alcohol	20	71.4%
Painkillers (Opioids/Opiates)	5	17.9%
Cocaine	4	14.3%
Marijuana	2	7.1%
Methamphetamines	2	7.1%
Anabolic Steroids	4	14.3%

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Table 4. History of substance (ab)use by primary TBI exposure groups.

Primary TBI exposure	Number of cases	% of respective group
Football	9	14.3%
Boxers	13	18.8%
Hockey	3	60.0%
Wrestling	2	66.7%
Veterans	2	33.3%
Other	1	14.3%
Total	30	19.6%

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from natural causes; however, the prevalence of suicide (11.7%) and accidental deaths (17.5%) is much higher in the CTE population than in the general population (1.5% and 4.8%, respectively) [52]. The greater percent of suicides and accidental deaths in the CTE case reports thus far have likely contributed to the lower average age of death in this selected group.

Suicide and accidental death are a more recent observation reported in subjects with CTE, with all suicides and 70% of accidental deaths coming after 2002. Researchers have suggested that reported CTE related symptoms such as lack of impulse control, criminal and antisocial behaviors, and mood disorders may be associated with the increased prevalence of suicide and accidental deaths [33]. A review by Iverson (2014), however, points out that suicide and accidental death have been reported more often in less advanced stages of CTE thereby suggesting that such behaviors may not be due to progression of CTE [53]. Selection-bias due to the greater CTE reporting on high profile former football players who have committed suicide or died due to accidental death has contributed to a possible overestimate of this cause of death. Published reports have noted both individuals and families of players who have died by suicide or accidental death have been disproportionately more likely to participate in CTE brain donation programs [2].

Neuropathology. Despite the younger average age of death in the CTE population compared to the general population, the typical age of death of subjects diagnosed with CTE can be considered advanced; hence, the effects of other age-related neuro degeneration diseases must also be taken into account [54,55]. The general pathological characteristics associated with CTE include macroscopic degenerative changes such as cavum septum pellucidum, generalized global atrophy, thinning of the corpus callosum, and ventricular dilatation. Neurofibrillary tangles similar to AD are seen but not the density of senile plaques which are generally observed in AD. Irregular, multifocal, and generally perivascular tau-immunoreactive neurofibrillary tangles (NFTs) are now considered a pathognomonic finding exclusive to CTE distinguishing it from other neurodegenerative diseases [3]. Beta-amyloid (A β) deposits are only identified in about 40% of those found to have CTE, as compared to extensive A β deposits present in nearly all those pathologically confirmed to have AD [5].

Large population studies reviewing pathological findings in the general population have shown that neurodegenerative pathological changes similar to CTE can occur naturally with the aging process. In a post mortem study with a non-selected cohort of 2661 subjects, Braak et al. reported that 91.6% of the subjects over the age of 60 had evidence of neurofibrillary tangles (NFT) [56]. Braak et al. as well as others have reported tau pathology findings in much younger cases, albeit at much lower frequencies compared to elderly subjects. In addition to tau related pathology, abnormalities in the transactive response (TAR) DNA binding protein with molecular weight of 43-kDa (TDP-43) have also been observed postmortem in the brains of CTE cases [26]. TDP-43 pathology is a proteinopathy similar to tauopathy that is commonly

observed in other neurodegenerative diseases such as in frontotemporal lobar degeneration (FTLD) and ALS. The findings of natural age-related pathology including both tau and TDP-43 have been commonly observed in elderly non-demented controls in a number of studies as well [57–59].

Age. Increasing age is also a major risk factor for other neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson Disease (PD), Lewy body dementia (DLB), and cerebrovascular disease (CVD) [55]. McKee et al. 2013 reported that the 20 oldest subject of their 68 CTE cohort also displayed CTE-related neurodegenerative changes consistent with AD, PD, and DLB among other diagnoses [2]. Although the interaction between diseases is unknown, one cannot discount that the presence of a co-morbid condition may distort both the clinical and pathological picture associated with CTE. As stated previously, CTE shares numerous neuropathological abnormalities commonly associated with other neurodegenerative diseases. Consequently, it is unclear what is responsible for specific clinical changes currently attributed to pre-morbid CTE [22,32]. Omalu et al. (2011) stated that caution should be exercised when diagnosing CTE in those over the age of 65 since normal age related changes in the brain, Alzheimer's disease, chronic ischemic changes and small vessel disease in the brain could lead to confusion with pathological CTE related changes.

Smith et al. [6] has proposed the pathogenesis of CTE may be best described as an interaction between neuropathological changes due to head trauma and natural age related changes of the brain. The exact contribution of prior head trauma on the clinical and neuropathological changes currently associated with CTE remains unclear and clinical symptoms may be a consequence of multiple neurodegenerative conditions including CTE. Importantly, the presence of neurodegenerative changes is not always associated with clinical symptomatic presentation [6].

Blaylock and Maroon postulated that immunoexcitotoxicity is a central mechanism in the development of CTE [60]. Based on this concept, microglia, which are activated following TBI, initiate injury response mechanisms resulting in the release of various cytokines, chemokines, reactive oxygen and nitrogen species as part of the innate inflammatory response. This is followed by a reparation and regeneration process—provided there is no recurrent blows to the head. With repetitive brain trauma, before the reparative process, immune mediators along with the traumatic release of excitatory intracellular glutamate can trigger a cascade of neuronal damage including dendritic retraction, synaptic injury, damage to microtubules, mitochondrial suppression and the over-production of tau.

Omalu et al. (2011) observed in an 18-year-old former high school football player “none to sparse” neurofibrillary tangles in the cerebral cortex, subcortical nuclei, and brain stem [3]. However he did conclude there was sufficient evidence of CTE but described these pathological findings as “incipient CTE”, and suggested such findings potentially represented an initial stage of CTE development. McKee et al. have described a CTE pathology staging system to standardize CTE findings. Stage I lists the earliest abnormalities observed for CTE as focal epicenters of pathological tau located in the frontal cortex [2]. By contrast, in more advanced CTE Stages III-IV the neuropathology is characterized by less focal and more widespread distribution of pathological tau throughout the cerebrum, subcortical nuclei, brainstem, and spinal cord. These neuropathologies are typically observed in older CTE subjects [2]. McKee et al. has also reported a correlation of greater neuropathologic changes with greater number of years played, thus suggesting more advanced CTE pathology is linked to increased exposure to head trauma, and exclusive to older age of death. Due to limited available data the natural progression of CTE is still unknown. Whether less-advanced cases of CTE reported in generally younger subjects would eventually progress to advanced neuropathologic findings associated with advanced CTE has not been documented. There are early reports that PET scanning for tau

protein may be useful to determine premorbid CTE and could possibly be used to follow changes over time [61].

Apolipoprotein E. Apolipoprotein E (ApoE) allele is a well-known genetic risk factor for Alzheimer disease. Kutner et al. and Jordan et al. have also reported that the presence of ApoE4 allele is associated with worse cognitive deficits in patients following severe head injury [62,63]. Data on ApoE genotype was available for 80 CTE cases, which represents the largest compilation of CTE ApoE genotype to date. A Chi-square goodness of fit test was used to compare ApoE genotype of this CTE population to the ApoE genotype of the general population (data adapted from Beydoun et al.) [64]. This analysis revealed no significant group difference between ApoE4 carriers in the CTE population and the general population ($p = .26$), suggesting that ApoE may not be a significant risk factor for the development of CTE. The result of this analysis is similar to findings by McKee et al. (2012) who also reported non-significant difference between ApoE genotype of the general population and the 68 cases of CTE in presented in their cohort [2]. The non-random selection and incomplete data of all CTE subjects limits speculation as to the significance of these findings. Further comparisons are needed to investigate the differences between post-mortem ApoE genotype of CTE, mTBI survivors and the general population.

Substance abuse. Thirty cases (20%) out of 153 CTE cases reported a positive history of substance abuse, which is greater than the 7.7% reported by Comptom et al. for substance abuse in US adults over their lifetime [65]. Cottler et al. (2011) reported that 52% of retired football players used opioids during their NFL career, of which 71% reported misuse [66]. CTE researchers have noted that the clinical presentation of CTE may be distorted due to history of substance abuse [2]. Research investigating neurodegenerative effects of substance abuse has shown that several commonly abused substances may potentiate the development of other neurodegenerative conditions [67–75]. These changes can include tau pathology, activated microglia, neuronal loss, and white matter rarefaction. In fact, in addition to these non-specific neurodegenerative changes, abuse of some substances such as opiates and opioids may elicit pathology very similar to those observed in CTE. In their research detailing the postmortem findings of opiate and opioid abusers, Anthony et al. (2010) observed enhanced NFT and NT deposition in their drug user subjects when compared to normal age-matched controls [74]. Notably, histopathological analysis revealed the enhanced tau pathologies observed in the drug users were analogous to the pathological tau found in AD and CTE, but as in the case of CTE, the distribution was determined to be distinct from classical AD progression. How substance abuse may influence, co-present, or alter the pathologies observed in CTE is unknown. Due to the limited number of CTE cases that include information about history of substance use/abuse as well as limited reporting on the extent of use/abuse, no conclusion can be made as to the presence and nature of an association between substance abuse and CTE.

CTE related clinical signs and symptoms. Due to a lack of consistent clinical data in the CTE case reports, this review did not specifically discuss the various premorbid clinical signs and symptoms reported with CTE. Reported CTE-related sign and symptoms include headache, difficulties with attention and memory, mood disorders, motor dysfunction and dementia [2,3]. McKee et al. have proposed a classification system (Stage I-IV) correlating advanced clinical findings to the degree of expected post mortem neuropathologic changes found with CTE [2]. (Table 5) For comparison, Table 5 includes the clinical symptoms of CTE as well as clinical symptoms of other common neurodegenerative conditions. This comparison demonstrates a significant overlap between signs and symptoms of CTE and other common neurodegenerative conditions. Based on this proposed classification it is difficult to distinguish symptomatic CTE from other neurodegenerative diseases such as Alzheimer's disease (AD),

Table 5. Clinical symptoms of CTE and other neurodegenerative conditions.

Symptoms	CTE (stages)				Presence in other neurodegenerative conditions			
	I	II	III	IV	PCS	AD	PD	FTLD
Asymptomatic	x	x	x					
Headache	x	x	x	x	x			
Attention/Concentration loss	x	x	x	x	x	x	x	x
Short-term Memory loss	x	x	x	x	x	x	x	x
Mood Disorder	x	x	x	x	x	x	x	x
Behavioral Problem	x	x	x	x		x	x	x
Executive Dysfunction	x	x	x	x		x	x	x
Language Difficulties	x	x	x	x		x	x	x
Visuospatial Difficulties			x	x			x	
Cognitive Impairments	x	x	x			x	x	
Suicidality		x	x	x		x		
Dementia			x	x		x	x	x
Motor Impairments		x	x	x		x	x	x

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Parkinson's disease (PD), and FTLT. Postmortem neuropathological assessment remains the standard for definitive diagnosis [2,3,6,76].

[Table 5](#) also compares clinical findings currently attributed to CTE to common signs and symptoms seen with post-concussion syndrome (PCS). In most cases, signs and symptoms associated with a concussion resolve within 1–4 weeks. PCS is characterized by a protracted course following the incident of mTBI that may last months to years following injury [77]. Reynolds et al. and others have demonstrated that over time therapeutic interventions, such as cognitive, visual and balance therapies can improve recovery rates in patients with persistent PCS [78]. Based on McKee's proposed clinical classification, symptoms of PCS substantially overlap with incipient symptoms of CTE. But unlike PCS where symptoms continue well after an mTBI, CTE attributed clinical findings are generally recognized as having a latent asymptomatic period of years to decades between exposure to mTBI and CTE symptom onset. Additionally, CTE, once symptomatic, is generally thought to be progressive and does not resolve over time [5]. Despite the differences in the general onset of these conditions, some researchers have reported PCS proceeding directly to pathologically diagnosed CTE, further skewing the clinical diagnosis of CTE [79].

Most cases of neuropathologically confirmed CTE have reported signs and symptoms of neurological decline prior to death. However, McKee et al. (2012) reported 11% of their CTE-positive cohort (n = 5) were asymptomatic for any neurological conditions. Asymptomatic presentation was reported as advanced as CTE Stage III where there is widespread NFT pathology and neurodegeneration [3]. Although asymptomatic presentation of neuropathology such as in AD is common, it remains unclear why some pathologically diagnosed CTE subjects experience symptoms while others do not.

American football players. Of the 153 CTE cases, 63 had a history of participation in football, and the majority of football subjects played at the professional level. It is important to separate out this subgroup since former football players have dominated CTE in the modern era of CTE research. In the 2012 review of 68 cases of CTE, McKee et al. observed that pathological findings of CTE were significantly correlated to the number of years a subject participated in football [2]. However, despite the professional levels making up the majority of CTE cases, high school football players have also been reported to have CTE in spite of their limited mTBI

exposure period. Although several of the high school football players were found to have CTE decades after their participation in high school football, three of the seven high school football players found to have CTE died prior to the age of 20. Despite this, the average age at death for football players is similar to the overall CTE cohort: 69% of CTE football cases compared to 75% of the remaining cases died prior to age 70. There was, however, a substantially higher prevalence of suicide in football players compared to the rest of the CTE cohort (17.5% ($n = 11$) vs. 5.26% ($n = 3$)). Football players account for 79% of all suicides case reports.

It is unknown whether this finding indicates that suicide is an at-risk behavior specifically related to former football players or if it is due to the bias associated with case reporting. Iverson et al. (2014) has noted that between the years 1960 and 2007 there were only nine cases of suicide of all former NFL players, again providing evidence that recent selective case reporting limits assertions as to risk factors associated with CTE [53].

Prevalence of substance abuse in American football players ($n = 9$; 14%) was lower compared to the rest of CTE cohort ($n = 21$; 23%). The limited data collected on substance abuse in the CTE literature prevents us to draw any firm conclusion about the association between CTE and substance abuse. However, it is of interest that the reported prevalence of substance abuse in former professional football players with CTE is substantially less than the prevalence suggested by other studies exploring substance abuse in former football players. For example, in a study by Cottler et al. (2011), 52% of retired football players used opioids during their NFL career with 71% reporting misuse [66]. What, if any, effect substance abuse contributes to CTE in football players remains unknown and requires further exploration.

Data on ApoE genotype was available for 53 out of the 63 football players (84.1%). A chi-square goodness of fit test was conducted to compare the prevalence of ApoE4 carriers in football mTBI subgroup with the general populations. The analysis revealed that the difference in frequency between the ApoE4 allele carriers in former football players with CTE and the general population was also non-significant ($p = .56$).

Is there a CTE epidemic?

The data compiled in this review is considerably limited due to the inherent limitations associated with retrospective case reports used to study CTE for the last 80 years. Case reporting lacks consistency in the types of data reported in CTE cases, such as incomplete pre-morbid data and furthermore, CTE case reports are inherently subject to selection bias. Despite the many millions who have participated in contact sports and potentially suffered an mTBI, there are currently only 40 modern era CTE articles with 153 pathologically confirmed CTE cases reported.

Although CTE research is still in its early stages, especially with American football players, researchers are encouraged to move beyond case reporting. These pioneering reports suggest an association between chronic neurodegeneration changes and head trauma, but without prospective controlled studies definitive conclusions about the incidence, prevalence and associated risk factors cannot be drawn.

Based on this review, beyond a history of prior head trauma, no other evidence was found to be associated with CTE related brain changes. Other previously suggested risk factors for CTE, such as severity and frequency of pre-morbid mTBI, history of substance abuse, duration of play in a contact sport, underlying genetic factors or uniqueness of pre-morbid symptoms, cannot be meaningfully associated with CTE at this time.

Although prior head trauma has been considered a consistent risk factor for CTE, Hazrati et al. (2013) demonstrated not all of those with prior sports related head trauma will have later onset of neurological deficits or develop neuropathology associated with CTE. They observed

that 3 out of 6 (50%) brains of former CFL athletes displayed CTE neuropathological abnormalities, although all 6 players had extensive histories of head injury [22]. Both Omalu et al. (2011) and McKee et al. (2012) observed similar findings in their cases where 6 out of 17 (35.3%) and 17 out of 85 (20%) subjects, respectively, were found negative for CTE neuropathologies, despite histories of multiple mTBI [2,3].

Conclusion

Our comprehensive review of the medical literature revealed 153 unique cases of pathologically confirmed CTE cases reported as of August 1, 2013. This figure comes after accounting for a large number of duplicate cases in the literature (43% of all cases), which misrepresents the current extent of research and hence our understanding of CTE. Additionally, this figure represents a very small fraction of the total number of individuals in contact sports—in the many millions—who may have suffered concussions or other mTBI.

This review has provided some clarity as to the demographics of the CTE cases reported to date, specifically countering the belief that premature death is associated with the diagnosis of CTE [80,81]. This review provides evidence that the recent increase of deaths due to suicide and accidental death, which are prevalent in recent former professional football players found to have CTE, is responsible for the lower average age of death found in this cohort.

There remains a lack of clarity with regards to neuropathological findings and pre-morbid clinical findings which overlap with many common neurodegenerative diseases [62]. CTE researchers are currently attempting to develop classifications for symptom and degree of neuropathological severity in order to improve the diagnosis of CTE. This is important as it relates to age-related neurodegenerative changes.

The case reports of CTE thus far have not conclusively identified risk factors associated with the development of CTE beyond a history of brain trauma. Head injury severity, frequency and occurrence of an associated concussion have not been routinely documented in the literature and therefore are of unknown contribution. Some reports have suggested that more years playing professional football may increase risk, but this suggestion has not been substantiated [2]. Preexisting genetic factors have been investigated as a possible contributing risk factor for the development of CTE. This review found that prevalence of ApoE4, a genetic marker for neurodegenerative diseases, is not significantly increased in the CTE cases to date compared to the general population [82,83].

Until recently, CTE was a pathological diagnosis primarily reported in former boxers. Since Omalu et al. reported the first CTE finding in a professional American football player in 2002 this formerly rare diagnosis has been thrust into a media, legal and research spotlight. Thus far, the described cases of CTE have exclusively been case reports or small series of cases. Several studies investigating small series of athletes with reported prior mTBI have found that although head trauma is a reported risk factor for CTE, not all individuals studied that experienced head trauma have been found to develop neuropathological changes associated with CTE [2,3,22].

This systematic review study emphasizes the need for further research into the epidemiology of CTE. Despite the lack of large scale systematic and randomized studies, the reporting of CTE in former professional American football players has led to wide spread speculation far beyond the conclusions that can be drawn based on the current state of CTE research. With CTE research in the early stages and the small number of current cases, there is no credible data with which to establish the incidence or prevalence of CTE in former contact sport participants.

Supporting Information

S1 PRISMA Checklist. PRISMA checklist for systematic review papers.
(PDF)

S1 Table. Complete overview of cases and demographics included in this systematic review.
(DOCX)

Author Contributions

Conceived and designed the experiments: JCM RW JB AA CM VM. Wrote the paper: JCM RW JB AA CM VM.

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BAILES

EXHIBIT 19

In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging

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Chronic traumatic encephalopathy (CTE) is an acquired primary tauopathy with a variety of cognitive, behavioral, and motor symptoms linked to cumulative brain damage sustained from single, episodic, or repetitive traumatic brain injury (TBI). No definitive clinical diagnosis for this condition exists. In this work, we used [F-18]FDDNP PET to detect brain patterns of neuropathology distribution in retired professional American football players with suspected CTE ($n = 14$) and compared results with those of cognitively intact controls ($n = 28$) and patients with Alzheimer's dementia (AD) ($n = 24$), a disease that has been cognitively associated with CTE. [F-18]FDDNP PET imaging results in the retired players suggested the presence of neuropathological patterns consistent with models of concussion wherein brainstem white matter tracts undergo early axonal damage and cumulative axonal injuries along subcortical, limbic, and cortical brain circuitries supporting mood, emotions, and behavior. This deposition pattern is distinctively different from the progressive pattern of neuropathology [paired helical filament (PHF)-tau and amyloid- β] in AD, which typically begins in the medial temporal lobe progressing along the cortical default mode network, with no or minimal involvement of subcortical structures. This particular [F-18]FDDNP PET imaging pattern in cases of suspected CTE also is primarily consistent with PHF-tau distribution observed at autopsy in subjects with a history of mild TBI and autopsy-confirmed diagnosis of CTE.

traumatic brain injury | chronic traumatic encephalopathy | [F-18]FDDNP PET | tau imaging | concussions

The consensus statement on concussions from the Fourth International Conference on Concussion in Sports (Zurich 2012) (1) defines acute mild traumatic brain injury (mTBI) or cerebral concussion as a brain injury with a complex pathophysiological process induced by biomechanical forces. Cerebral concussion causes white matter axonal injury due to axonal shearing and stretching (2), typically resulting in the rapid onset of short-lived impairment of neurological function that resolves spontaneously and largely reflects a functional disturbance rather than a structural injury. As such, no abnormality is seen on standard structural neuroimaging determinations (1).

A number of early literature reports described a neurodegenerative disease associated with a history of repetitive TBI in retired professional boxers (3, 4), with a prevalence rate of up to 47% among retired professional boxers aged 50 y and older who boxed for more than 10 y (5). Initially named “punch drunk syndrome” (3) and dementia pugilistica (4), this syndrome is now known as chronic traumatic encephalopathy (CTE) in the current literature (6, 7).

Compelling autopsy evidence (6–8) and neurobehavioral determinations (9) of retired professional American football athletes indicate that a subgroup develops neurodegenerative and clinical changes typical of CTE, a progressive syndrome distinctively different from Alzheimer's disease (AD), which is the most common form of dementia in the elderly (10). The connection

between multiple concussions and subconcussive head impacts (2) and CTE is compelling, because history of repetitive concussions is the strongest risk factor for development of CTE in numerous contact sports (e.g., American football, rugby, boxing, ice hockey, soccer, and professional wrestling), in war veterans with a history of blast or blunt force TBI, and in conditions where trauma to the head occurs for various reasons (e.g., falls during seizures, head-banging in autistic children, motor vehicle and domestic accidents, domestic violence and abuse) (6, 8, 11–14). As with most neurodegenerative diseases, clinical diagnosis remains elusive due to the lack of specificity of CTE clinical symptomatology criteria, and histopathological examination of brain at autopsy is the most definitive diagnostic modality (6, 8, 11).

The novel imaging approaches leading to the in vivo characterization of CTE brain neuropathology premortem (e.g., PET) are complementary to structural imaging modalities [e.g., diffusion tensor imaging MRI (DTI MRI)] and offer a specific and sensitive strategy to facilitate diagnosis of CTE. Neuronal and glial fibrillar hyperphosphorylated microtubule-associated protein tau deposits composed of paired helical filament (PHF)-tau are the primary brain proteinopathy of CTE based on autopsy determinations, and their 3R/4R tau isoform ratio is similar to that of AD (11). Their topographically predictable pattern of distribution was used as a basis for a severity staging system of CTE neuropathology (7), ranging from mild (neuropathology

Significance

Mild traumatic brain injuries are frequent events in the general population and are associated with a severe neurodegenerative disease, chronic traumatic encephalopathy (CTE). This disease is characterized by abnormal accumulation of protein aggregates, primarily tau proteins, which accumulate in brain areas responsible for mood, fear, stress, and cognition. There is no definitive clinical diagnosis of CTE at the present time, and this new work shows how a tau-sensitive brain imaging agent, [F-18]FDDNP, may be able to detect the disease in living people with varying degrees of symptoms. Early detection would facilitate the most effective management strategies and provide a baseline to measure the effectiveness of treatments.

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Conflict of interest statement: J.R.B., G.W.S., and S.-C.H. are coinventors of the [F-18]FDDNP PET technology that is covered under University of California, Los Angeles patents and licensed to TauMark, LLC. J.R.B., G.W.S., R.P.F., and B.O. have a financial interest in TauMark, LLC.

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stages I and II) to advanced (neuropathology stages III and IV) (7) (Tables S1 and S2). In addition, more than 80% of analyzed pathologically confirmed CTE cases also show transactive response (TAR) DNA-binding protein of ~43 kDa (TDP-43) either as inclusions in sparse neurites in cortex, medial temporal lobe structures, and brainstem in CTE neuropathology stages I–III, as widespread neuronal and glial inclusions in severe CTE cases (neuropathology stage IV), or in CTE cases with motor neuron disease (7, 15) (Tables S1 and S2). CTE cases also can exhibit the presence of other fibrillar protein aggregates. McKee et al. (7) and Omalu et al. (8) reported that in autopsy determinations, less than half of all CTE cases and less than one third of “pure” CTE cases show amyloid- β (A β) deposits, predominantly as scattered cortical diffuse plaques in low density (Tables S1 and S2). Of note is that subjects with A β deposits were significantly older than those without. Moreover, their neuropathology was more severe than that in cases without A β deposits and was often combined with α -synuclein deposits (7). As an example, as reported by McKee et al. (7), of 30 CTE cases with at least some cortical A β deposits (of 68 confirmed CTE cases), 29 brains were from subjects who died in their seventh decade of life and one from a subject who died in his sixth decade.

Subsequent to our preliminary report (16), in this work we use [F-18]FDDNP, an imaging agent for fibrillar insoluble protein aggregates (16–20), and PET imaging with the aim of establishing (i) topographic brain localization of [F-18]FDDNP PET signals indicative of fibrillar neuroaggregates in retired professional American football players with suspected CTE (mTBI group) vs. controls (CTRL); (ii) determination of [F-18]FDDNP PET signal patterns in the mTBI group; (iii) presence of [F-18]FDDNP PET signal as a measure of neuropathology in the brain areas involved in mood disorders related neurocircuits; (iv) correlation of [F-18]FDDNP PET results with neuropathology distributions in confirmed CTE cases; (v) differential patterns of [F-18]FDDNP PET signals, and thus deposition of fibrillar neuroaggregates, in the mTBI group with respect to the AD group; and (vi) preliminary demonstration of differences in [F-18]FDDNP PET signal patterns in mTBI cases with different etiology, i.e., contact-sport-related mTBI in retired professional American football players vs. blast-induced mTBI in war veterans. We further intended to demonstrate that tau (vs. A β) specificity of high affinity PET molecular imaging probes may not be a necessary requirement when used in CTE subjects with primary proteinop-

athy in the form of PHF-tau (8): PET imaging probes potentially sensitive to TDP-43 aggregates and A β deposits, which are present in higher densities almost exclusively in older CTE cases with more advanced neuropathology (e.g., stage IV), could better define disease progression based on quantification of differences in regional loads of combined neuropathologies because additional neuropathologies appear in predictable topographical and temporal patterns.

Results

Brain [F-18]FDDNP PET Patterns in Suspected CTE (mTBI Group). In all types of neurodegenerative proteinopathies, including CTE, pathology-based diagnosis using protein specific immunohistochemistry (IHC) does not result only from the presence of protein pathology in the brain, but rather from detection of disease specific topographic patterns of pathology distribution combined with quantitation of regional and global pathology loads. Molecular imaging agents targeting such fibrillar protein pathologies must therefore accurately and reliably detect these disease-specific patterns of distribution and their changes both in the pattern complexity and in regional pathology loads that may evolve due to the progressive nature of these neurodegenerative diseases.

Demographic data for all mTBI group subjects are provided in Table 1. We identified four distinctive topographical patterns of brain [F-18]FDDNP PET signal in the mTBI group, which are presented in increasing complexity from T1 to T4 in Fig. 1 (*Upper*) in three views (transaxial, top row; sagittal, middle row; and coronal, bottom row). All four patterns distinguish the mTBI subjects from cognitively intact control subjects (CTRL group) (Fig. 1, *Upper*, and Table 2).

The observed [F-18]FDDNP PET signal patterns are defined as follows:

- i) Pattern T1 is predominantly subcortical in brainstem (mid-brain) with localized involvement of the limbic medial temporal lobe structures (limited to amygdala).
- ii) Pattern T2 shows [F-18]FDDNP PET signal in all subcortical areas analyzed in this study, in all limbic medial temporal lobe areas [amygdala and medial temporal lobe (MTL); hippocampus, entorhinal cortex, parahippocampal gyrus], and in parts of the frontal cortex including anterior cingulate gyrus (ACG).
- iii) Pattern T3 shows further increases in signal intensity and pattern complexity: all affected areas in the T2 pattern plus

Table 1. Demographic information for the mTBI group

Subject	Age (y)	Education (y)	Race	Active career (y)	Position	Retirement (y)	Diagnosis	MMSE (score)	HAM-D score	HAM-A score
TBI01	59	18	AA	16	Linebacker	28	MCI-MD	25	11	13
TBI02	64	17	C	10	Quarterback	38	Normal	30	5	6
TBI03	73	18	C	16	Offensive guard	44	Dementia	17	8	5
TBI04	50	15	C	14	Defensive tackle	20	MCI-MD	28	17	12
TBI05	45	18	C	12	Center	16	MCI-A	29	6	0
TBI06	86	16	C	11	Running back	58	MCI-A	27	3	3
TBI07	62	16	C	17	Offensive guard	28	MCI-NA	27	16	19
TBI08	51	18	AA	14	Defensive lineman	22	MCI-MD	30	17	31
TBI09	59	15	AA	16	Running back	26	MCI-MD	27	14	12
TBI10	54	14	AA	12	Wide receiver	22	MCI-MD	25	15	16
TBI11	40	16	C	17	Center	7	MCI-A	27	17	21
TBI12	54	16	C	16	Offensive lineman	20	MCI-A	26	0	1
TBI13	62	16	AA	13	Offensive lineman	32	MCI-A	28	33	30
TBI14	54	16	C	9	Nose tackles	25	MCI-MD	26	21	22

A, amnesic; AA, African American; C, Caucasian; HAM-A, Hamilton Anxiety Score (mild to moderate symptoms: 18–24; moderate to severe: > 24); HAM-D, Hamilton Depression Score (mild symptoms: 8–16; moderate to severe: > 16); MCI, mild cognitive impairment; MD, multiple domains; MMSE, mini-mental state examination (dementia range <24); NA, nonamnesic.

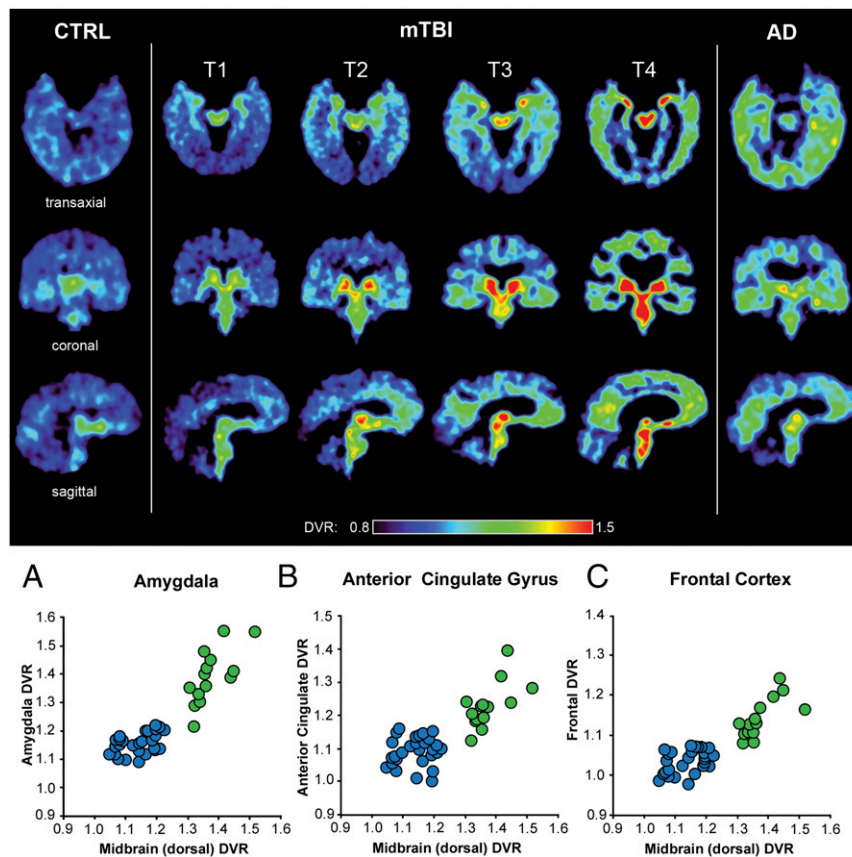


Fig. 1. (Upper) [F-18]FDDNP distribution volume ratios (DVR) parametric images showing patterns T1 to T4 of increased [F-18]FDDNP signal observed in the mTBI group compared with cognitive control subjects (Left). The T1 pattern shows involvement of two core areas which have consistently increased [F-18]FDDNP signal in all four patterns: amygdala (limbic) and dorsal midbrain (subcortical). Patterns T2 to T4 are marked by increase of [F-18]FDDNP signal in these two core regions and progressively larger number of subcortical, limbic, and cortical areas. Although more complex patterns (e.g., T4) overlap with AD in the cortex, midbrain and amygdala signals are elevated above the levels in AD (Table 2). An AD case is shown in the right column for comparison. (Lower) A is a 2D scatter plot showing [F-18]FDDNP DVR values in two core areas consistently involved in CTE (subcortical structures (dorsal midbrain) and limbic structures (amygdala)), clearly demonstrating separation of mTBI and CTRL groups. B and C demonstrate similar separation effect when dorsal midbrain is compared with cortical areas typically associated with CTE and its mood disorders, namely anterior cingulate gyrus (ACG) (B) and frontal lobe (C). mTBI subjects are represented by green circles, and CTRL subjects are represented by blue circles. See *SI Materials and Methods* for additional correlations of [F-18]FDDNP PET DVR values in dorsal midbrain and amygdala with several cortical and subcortical areas (Fig. S1).

additional cortical areas [posterior cingulate gyrus (PCG), lateral temporal lobe (LTL), and parietal lobe]; this pattern is not associated with severe ventricular enlargement and prominent cortical atrophy commonly observed in aged retired boxers with dementia pugilistica.

- iv) Pattern T4 shows high [F-18]FDDNP PET signal throughout the cortical, subcortical, and limbic medial temporal lobe structures, as well as in the white matter areas; this pattern was associated with significant brain atrophy (MRI or CT); possible comorbidity of CTE with other neurodegenerative diseases may be suspected, e.g., AD or end stage CTE progressing to, and simulating, AD.

All mTBI subjects ($n = 14$) were treated as a single group for further group comparison with the CTRL group ($n = 28$). Analysis of [F-18]FDDNP PET signal patterns T1–T4 identified the dorsal midbrain and amygdala as two core regions with consistently increased [F-18]FDDNP PET signals, which separated the mTBI group from the CTRL group as shown in the 2D correlation graph in Fig. 1A (Lower). Statistical analysis (ANOVA with post hoc Tukey–Kramer test; Table 2) shows a high degree of statistical significance ($P < 0.0001$) for group separation in both areas and for a positive correlation between these two areas within the mTBI group (Spearman rank correlation coefficient: $r_s = 0.745$, $P < 0.01$; Table S3).

All subcortical and limbic medial temporal lobe areas have also met strict criterion for good separation of mTBI and CTRL groups (Tukey–Kramer test at $P < 0.0001$) (Table 2). Other subcortical areas also show positive Spearman rank correlations with both core regions (Fig. S1 and Table S3) reflective of similar trends of increasing regional [F-18]FDDNP distribution volume ratio (DVR) values with increasing [F-18]FDDNP PET signal pattern complexity from T1 to T4. However, some subcortical structures like thalamus and caudate/putamen in mTBI subjects show increased DVR values only in more severe cases.

In contrast to subcortical regions, cortical areas showed different trajectories of involvement in the [F-18]FDDNP PET signal patterns T1–T4 with a clear anterior–posterior gradient. This difference in cortical trajectories is reflected in separation of the mTBI and CTRL groups only in the ACG (Fig. 1B, Lower, and Fig. S14) and frontal lobe (Figs. 1C, Lower, and 2A, z axis, and Table 2). Spearman rank correlations within the mTBI group were determined for combinations of all analyzed regions that have shown mTBI–CTRL group separations (and involvement in the [F-18]FDDNP PET signal patterns T1–T4) and correlations of the core regions (amygdala and dorsal midbrain) with a large number of subcortical regions [brainstem (pons), diencephalon (thalamus), and basal ganglia (striatum)]

Table 2. [F-18]FDDNP DVR group mean values for mTBI group (14 subjects), control group (28 subjects), and Alzheimer’s disease group (24 subjects)

	Limbic		Subcortical						Cortical					
	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	OCC
mTBI	1.397 (0.095)	1.183 (0.042)	1.330 (0.090)	1.373 (0.060)	1.429 (0.082)	1.507 (0.107)	1.319 (0.071)	1.531 (0.104)	1.144 (0.049)	1.230 (0.068)	1.095 (0.047)	1.160 (0.077)	1.122 (0.048)	0.997 (0.050)
CTRL	1.162 (0.036)	1.112 (0.023)	1.135 (0.057)	1.138 (0.055)	1.234 (0.049)	1.250 (0.086)	1.156 (0.064)	1.322 (0.069)	1.039 (0.033)	1.093 (0.043)	1.054 (0.026)	1.082 (0.040)	1.064 (0.026)	1.021 (0.048)
AD	1.242 (0.060)	1.189 (0.020)	1.137 (0.062)	1.164 (0.078)	1.229 (0.058)	1.318 (0.109)	1.145 (0.075)	1.345 (0.090)	1.112 (0.027)	1.141 (0.073)	1.148 (0.030)	1.180 (0.022)	1.155 (0.024)	1.059 (0.056)
ANOVA														
F value	59.82*	73.26*	29.26*	26.56*	24.36*	15.01*	13.97*	21.82*	45.83*	13.72*	72.00*	44.93*	82.04*	5.43
Student t test														
mTBI-CTRL	*	*	*	*	*	*	*	*	*	*	*	*	*	*
mTBI-AD	*	NS	*	*	*	*	*	*	NS	NS	NS	NS	NS	NS
AD-CTRL	*	*	NS	NS	NS	NS	NS	NS	*	NS	*	*	*	NS
Tukey-Kramer test														
mTBI-CTRL	*	*	*	*	*	*	*	*	*	*	NS	NS	NS	NS
mTBI-AD	*	NS	*	*	*	NS	*	*	NS	NS	NS	NS	NS	NS
AD-CTRL	*	*	NS	NS	NS	NS	NS	NS	*	NS	*	*	*	NS

Mean group DVR values (SD values given in parentheses). ACG, anterior cingulate gyrus; Amygd, amygdala; F, frontal; Hypo-Th, hypothalamus; LTL, lateral temporal lobe; Midb-D, dorsal midbrain; Midb-V, ventral midbrain; MTL, medial temporal lobe; NS, not significant ($P \geq 0.0001$); Occ, occipital; P, parietal; PCG, posterior cingulate gyrus; Str, striatum (caudate nucleus and putamen); Th, thalamus (medial thalamus). * $P < 0.0001$; NS, not significant ($P \geq 0.0001$).

and cortical regions (frontal, ACG, LTL, parietal) were all found to be significant ($P < 0.05$; Table S3). It is noteworthy that these structures—brainstem (midbrain, pons), limbic medial temporal lobe (amygdala), and frontal lobe (frontal cortex, ACG)—are interconnected by brain circuitry supporting normal mood and behavioral functioning (21), which is perturbed early in subjects with a history of multiple concussions (2, 22).

Results of ANOVA statistical tests for separation of DVR values in all three groups are given for all areas analyzed, and areas that meet the Tukey-Kramer test criterion of $P < 0.0001$ are identified for comparisons of the mTBI group with the CTRL and the AD groups separately (Table 2). Tables S4 (mTBI group), S5 (CTRL group), and S6 (AD group) show all regional DVR values for all subjects in all groups. Tables S7

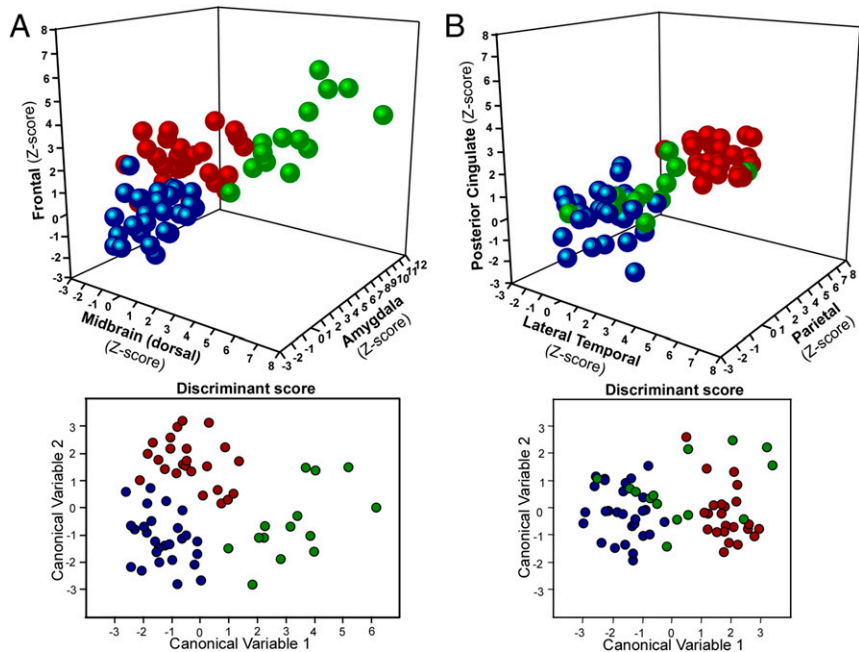


Fig. 2. [F-18]FDDNP PET DVR value analysis separates mTBI, CTRL and AD groups. (A) A 3D scatter plot correlation of subcortical regions (dorsal midbrain) with limbic structures (amygdala) and cortical regions (frontal lobe) shows that all three groups (mTBI, green; AD, red; CTRL, blue) can be effectively separated based on the differences in binding patterns in these three areas. The mTBI group is significantly separated from control group in all three areas and from the AD group in the limbic and subcortical areas (Table 2). (B) A 3D scatter plot correlation of cortical structures alone, without comparison with subcortical or limbic structures, demonstrates that the mTBI group overlaps both with AD and CTRL groups. Results of discriminant analysis for the correlation of three areas depicted in each 3D scatter plot are shown underneath each graph.

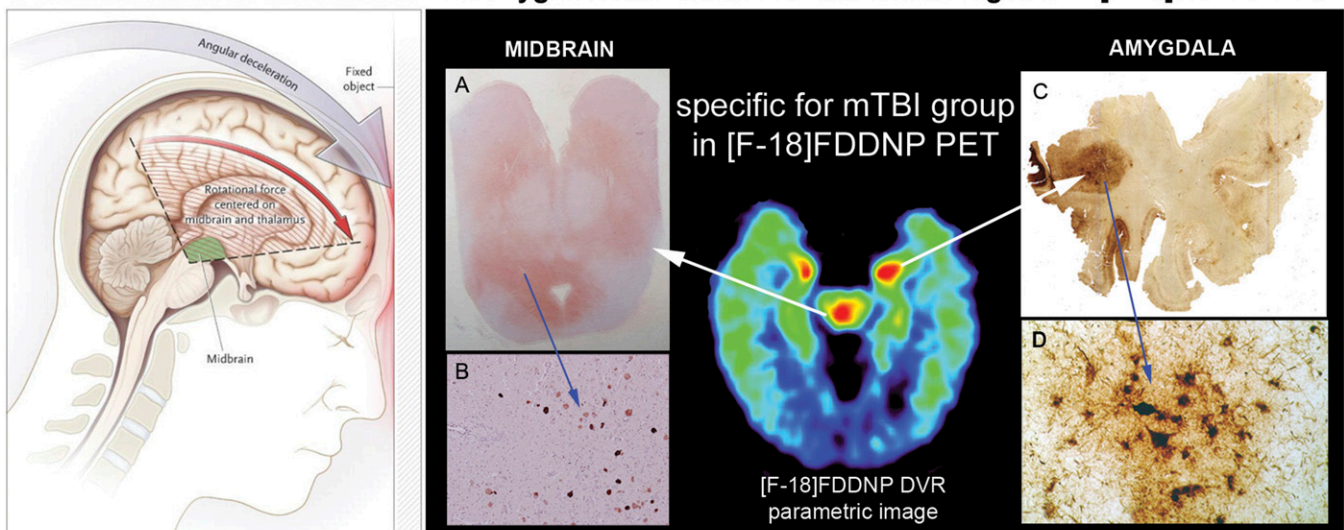
(mTBI group), S8 (CTRL group), and S9 (AD group) show all regional Z-score values for all subjects in all groups.

[F-18]FDDNP Results: Correlation with Autopsy of Confirmed CTE Cases. [F-18]FDDNP PET signal patterns T1–T4 are consistent with pathology reports showing involvement of subcortical structures (e.g., locus coeruleus, substantia nigra, dorsal raphe, thalamus, basal ganglia), limbic medial temporal lobe structures (amygdala and MTL), and frontal cortex (6–8, 10, 11, 23). The F-18]FDDNP PET signal in the subcortical structures is in accordance with the examples of tau IHC labeling of pons, midbrain, thalamus, and basal ganglia in CTE shown on large brain tissue samples in refs. 7, 10, 11, and 23 (Fig. S2, *Left*). Presence of tau IHC in subcortical regions is further supported by our evidence from confirmed CTE cases that were not scanned with [F-18]FDDNP PET (Fig. 3*II* and Fig. S2, *Right*). Midbrain and amygdala are unique brain regions with elevated [F-18]FDDNP signals found in all 14 mTBI subjects. DVR values shown in Table S4 suggest that

the PET signal is not uniformly distributed throughout all midbrain structures. A dorsal-ventral gradient observed with PET imaging agrees well with tau IHC results (Fig. 3*II, Left*), which shows high IHC density in the periaqueductal gray in dorsal midbrain and lesser IHC levels in substantia nigra, red nucleus, and other nuclei situated in the ventral midbrain (Fig. S2, bottom example in the left panel) (11). Similarly, high [F-18]FDDNP signals in the amygdala and other limbic medial temporal lobe structures coincide with common CTE autopsy observations of high involvement of amygdala and MTL shown in deceased retired professional American football players (Fig. 3*III*) (7, 23).

[F-18]FDDNP PET in mTBI vs. AD. From a perspective of clinical diagnosis, CTE can be mistaken for AD, particularly at later stages (24). However, the pattern of subcortical and limbic medial temporal lobe (amygdala vs. MTL) [F-18]FDDNP signal distribution in AD is quite different from that of concussion-based mTBI (suspected CTE) (Figs. 1 and 2 and Fig. S1) (25). To

I. Biomechanics of concussion II. Amygdala and Dorsal Midbrain: core regions in [F-18]FDDNP PET



III. Robust tau IHC in amygdala and MTL is consistently present in symptomatic retired football players

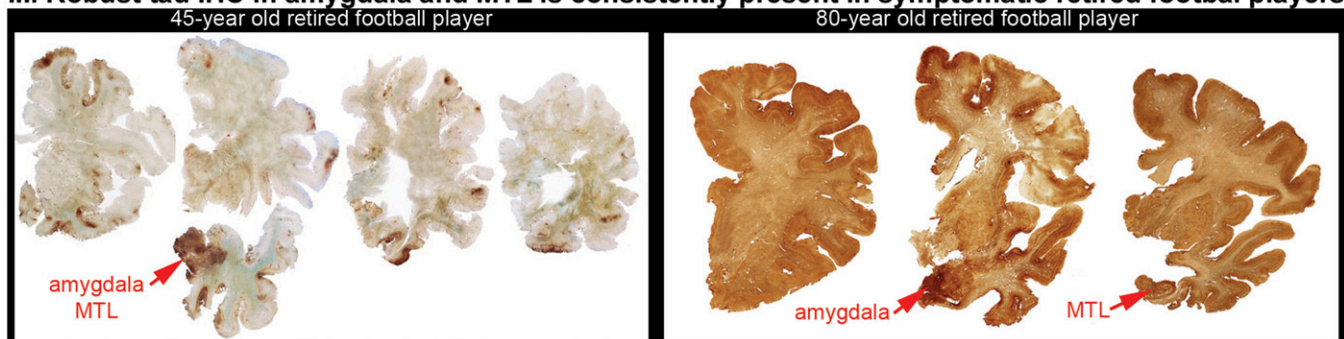


Fig. 3. Involvement of amygdala and midbrain areas in concussion-based mTBI is supported by both mechanistic concept of injury (*I*) and by the results of neuropathological examinations in deceased retired American football players with premortem complaints of functional impairments (*II* and *III*). (*I*) Rotation of the brain in the sagittal plane during a concussion, associated with significant accelerations and deceleration, will have significant negative effect on the brain tissue in the midbrain and thalamus (green shaded area) and on the affected cortical areas (red area). Stretching, compression, and shearing of axons during such sudden brain movements is hypothesized to be the cause of axonal injury (reprinted from ref. 33; reproduced with permission from Massachusetts Medical Society). Online version of ref. 33 also contains an animated version of this figure (www.nejm.org/doi/full/10.1056/NEJMcp064645). Similarly, rotation in the coronal plane has been shown to lead to consistent damage to midbrain region tracts (27). (*II*) A–D show results of tau immunohistochemistry and demonstrate that in the mTBI group areas of increased [F-18]FDDNP signal in amygdala and dorsal midbrain coincide with presence of dense tau deposits in periaqueductal gray (PAG) in dorsal midbrain (A and B) and in amygdala (C and D; reprinted from ref. 21; reproduced with permission from Wolters Kluwer Health). (*III*) Amygdala and MTL areas are affected in the brains of retired professional American football players who died due to suicide (*Left*; 45-y-old retired player; reprinted from ref. 21; reproduced with permission from Wolters Kluwer Health) or due to natural causes [*Right*; 80-y-old retired NFL player; © Oxford University Press (brain.oxfordjournals.org/content/136/1/43) (reprinted from ref. 11)]. Amygdala and MTL areas are the first areas with high density of tau deposits in the neocortex and remain one of the most affected cortical regions in the majority of retired professional American football player cases.

facilitate visual comparison of AD and mTBI groups, we converted all DVR values in these two groups to Z-scores defined as $Z\text{-score} = (\text{DVR}_{(\text{ROI-X})} - \text{DVR}_{(\text{CTRLgroup-mean})}) / \text{SD}_{(\text{CTRLgroup})}$. CTRL group DVR mean values and SDs for each region of interest (ROI) are provided in Table 2. All graphs in Fig. 2 and Fig. S1 are shown on Z-score scales. Using the Tukey–Kramer test criterion of $P < 0.0001$, it is quite clear that the mTBI group is separated from the AD group in the majority of subcortical areas and in amygdala but not in cortical areas, which is not surprising because AD is predominantly a cortical disease in terms of pathology accumulation. In the presence of significant cortical [F-18]FDDNP signals in both groups, our evidence shows that we can completely separate both groups using a combination of both core regions (amygdala and dorsal midbrain; x axis and y axis in the 3D graph in Fig. 24).

The following general observations can be made:

- i) The AD group showed [F-18]FDDNP DVR values similar to the CTRL group in subcortical regions (Table 2 and Fig. S1 C–F). Both the CTRL and AD groups had increased variability in [F-18]FDDNP DVR values in subcortical regions compared with cortical and limbic areas (Table 2). In contrast to subcortical regions, the AD group showed significantly higher signals than did the CTRL in cortical areas, with the exception of occipital lobe and the ACG (Table 2 and Fig. 2B). The results were consistent with our previous reports on [F-18]FDDNP PET imaging in AD (18).
- ii) The mTBI group showed higher DVR values compared with the AD group in all subcortical areas (Table 2 and Fig. S1 C–F), which is most clearly observed in more complex [F-18]FDDNP PET signal patterns T2–T4. Similarly, amygdala (a limbic medial temporal lobe area) also demonstrated significantly higher involvement in the mTBI group than in the AD group, which is consistent with pathology observations in neuropathology stages III and IV (7). By contrast, other limbic medial temporal lobe structures (MTLs) showed DVR values in the mTBI group that were comparable to those in the AD group. Fig. 24 presents a 3D scatter plot of Z-scores with limbic medial temporal lobe structures (amygdala), subcortical (dorsal midbrain), and cortical structures (frontal) demonstrating a good separation of the mTBI group from the AD and CTRL groups. Fig. S1 illustrates similar correlative measures under the Tukey–Kramer test criterion of $P < 0.0001$ involving subcortical, limbic, and selected cortical structures, which provided distinctive separation of the mTBI group from AD and CTRL groups.
- iii) As previously reported (18), the AD group showed significantly higher [F-18]FDDNP signals in all cortical areas, and significant overlap with the mTBI group was observed in all cortical regions including MTL (Table 2, Fig. 2, and Fig. S1A). As predicted from the clinical symptomatology (mood vs. cognitive), the mTBI group showed predominant involvement in the frontal and ACG ROIs compared with the AD group. Fig. 2B further demonstrates that cortical [F-18]FDDNP PET signals do not discriminate between the mTBI and AD groups, whereas subcortical or limbic signals do. This lack of cortical discrimination becomes more obvious in the more severely affected and older (7) suspected CTE subjects (pattern T4).

These [F-18]FDDNP PET observations are consistent with the hypothesis that in individuals with suspected CTE, initial selected vulnerability is present in those circuits involving subcortical and limbic structures, including limbic structures in the medial temporal lobe. Through the medial temporal lobe and nodes in the prefrontal lobe (23), these circuits are connected with cortical areas involved in cognition via the default mode network (DMN), which includes the medial temporal lobe structures, the medial prefrontal cortex, posterior cingulate gyrus, and pre-

cuneus and parietal cortex, which may provide a predictable pathway for tau progression in CTE through cortical areas. In AD, tau and A β deposition are observed relatively early in the medial temporal lobe structures and the cascade of cortical pathology deposition typically follows the DMN with relatively lesser involvement of mood circuits in subcortical and limbic areas (18, 25, 26), which provides the basis for differentiation of the mTBI and AD groups.

Discussion

Biomechanical Models of Concussions, Subject Population, and Brain Pathology. TBI has a profound medical and social impact, and it may occur under a variety of circumstances, from domestic accidents to war-related events. A concussive brain injury results from rapid rotational and translational accelerations and decelerations as well as impact decelerations, which exert significant forces on brain tissue and cause membrane and axonal injuries without overt gross bleeding or focal parenchymal damage (27). Following axonal and membrane cellular injury, isomorphic astrogliosis and microglial activation occur, which further interferes physically and chemically with regeneration and repair of disconnected axons (28), and leads to PHF-tau and TDP-43 deposition by a yet unknown mechanism. Because inflammation and white matter degeneration can persist for years (29), the brain is increasingly vulnerable to reinjury via traumatic axonal injury (30). Focal types of brain injury such as contusions or lacerations that commonly occur in moderate and severe traumatic injuries in humans or primate models of traumatic brain injury (27, 31, 32) are only rarely reported in concussions (33).

As such, American football players present a relatively homogeneous group based on the type of concussions and subconcussions frequently present in this subject population (2). The initial, pioneering observation by Omalu et al. of extensive tauopathy deposition in the brains of American football players (8, 34), involving subcortical, limbic areas, and brain cortices, led to the unequivocal demonstration of CTE as a unique clinical entity (35). Most recent detailed studies by McKee et al. (7, 11, 21) provided confirmatory results of the unique pathological characteristics of CTE. In a study describing 85 brains including American football players, boxers, and veterans, among others, McKee et al. demonstrated the extensive tau aggregate distribution in subcortical and limbic structures, as well as cerebral cortices, in 68 brains with pathologically confirmed CTE in various stages of the disease (7).

In CTE cases resulting from playing American football, tau deposits consist of PHF-tau IHC positive neuronal neurofibrillary tangles (NFTs) and neuropil threads, as well as astrocytic tangles. Distribution of PHF-tau IHC positive structures follows a pattern that increases in complexity both with age and symptom severity (6, 7, 11, 21). In cases of CTE with advanced pathology (stages III and IV) (7), dense deposits of tau pathology were consistently found predominantly in subcortical structures and limbic areas of frontal and temporal lobes with extension to cortical areas. A β aggregates are not frequently a distinctive pathological feature of CTE, with less than 50% of the cases presenting predominantly scattered sparse deposition of cortical A β in diffuse form, most frequently in later stages of pure CTE (stage IV) (7, 11). Often other protein aggregates, such as TDP-43 in more than 80% of all pathologically confirmed CTE cases, and more rarely α -synuclein, can be present as secondary proteinopathies, also most prominently in later stages of the disease. TDP-43 is present in high density in midbrain of all CTE patients with motor neuron disease, but it is more variable in CTE patients stages I–III without motor neuron disease (7, 15, 21) (for topographic details of different pathologies in various disease stages see Fig. S2 and Tables S1 and S2). Thus, it cannot be discounted that some of the [F-18]FDDNP signal in the brainstem, thalamus, and basal ganglia of the mTBI group, particularly in disease stages with more advanced pathology and

increased deposit densities (stage IV) (7), originates from the presence of TDP-43. TDP-43 contains amino acid sequences that make it aggregation prone in vitro and also in vivo because a portion of neuronal and glial TDP-43 inclusion bodies in motor neuron disease and CTE appear as filamentous structures (36) but are generally not considered amyloid due to missing amyloid specific thioflavin-S fluorescent stain. Recent evidence shows that at least some of these inclusion bodies do show the typical thioflavin-S staining, which provides evidence for presence of amyloid fibrillar structures within them (36).

Brain-Specific Neuropathology Accumulation Measured with [F-18]FDDNP PET. This work offers compelling evidence of the ability of [F-18]FDDNP PET to detect neuropathology in the living brain of American football players in a manner consistent with the pattern of deposition found at autopsy (6, 7, 34). [F-18]FDDNP has a high affinity for tau fibrils ($K_D = 36.7 \pm 11.6$ nM vs. $K_D = 5.52 \pm 1.97$ nM for A β 42 fibrils) (37), which provides a high binding potential (BP; defined as R/K_D ; where R = number of tau aggregate binding sites per volume of brain tissue) for tau imaging visualization in vivo (38). The very low regional density of other proteinaceous β -sheet-containing aggregates (e.g., TDP-43, diffuse A β) would result in a low [F-18]FDDNP binding potential for non-tau aggregates, below the limit of sensitivity of PET, in the earlier CTE stages (stages I and II) as previously shown with the low abundance of α -synuclein in a Lewy body dementia patient (17). However, the ability of [F-18]FDDNP PET to detect A β becomes important to help in the characterization of AD comorbidity when it is present, particularly in advanced neuropathology CTE stages (stage IV) when proteinaceous neuropathologies are widespread, and quantitation of total neuropathology load can reflect additional pathology burden due to comorbid conditions. This investigation further confirms the unique sensitivity of [F-18]FDDNP to tau aggregates in vivo, as demonstrated by earlier work in patients with a neurodegenerative tauopathy, progressive supranuclear palsy (PSP) (19). All these studies in humans are supported by the demonstration of the ability of the 6-dialkylamino naphthalenyl-2-cyanoacrylate scaffold (present in FDDNP) to bind tightly to tau aggregates as previously shown by X-ray analysis of crystals obtained by cocrystallization of DDNP with tau segments (39), in vitro binding affinities with tau fibrils, tau rodent models, and postmortem autopsy results and comparisons with premortem scans (16, 17).

These findings of brain tau accumulation and distribution in this subject population are also consistent with earlier observations that subcortical structures such as brainstem and thalamus are considered as the fulcrum or center point of force vectors that bear the maximal rotational forces in American football players receiving concussions (Fig. 3) (2, 33). Axonal degeneration due to thousands of cranial impacts resulting in concussive and subconcussive injuries leads to other neurodegenerative changes including PHF-tau deposition throughout the areas of selective vulnerability in heavily interconnected cortico-striato-pallido-thalamic loops that support emotions, mood, and behavior (for a review of this topic, see ref. 22). Initial widespread involvement of the limbic areas of the medial temporal lobe (followed by the frontal lobe) is also observed in the subjects studied in this investigation and defines core regions that are consistently affected as neuropathology distribution increases in complexity during CTE evolution (Fig. 1, *Upper*).

These [F-18]FDDNP PET imaging patterns are observed in all cases studied thus far, suggesting a “fingerprint” PET scan of neuropathology accumulation that is characteristic of CTE. This [F-18]FDDNP PET imaging topographic distribution, moreover, is quite different from that found in AD (Fig. 2) and is consistent with profiles of neuropathology distribution described by Omalu et al. (6) and McKee et al. (7) in autopsy specimens with confirmed CTE. Omalu et al. defined four distinct pathology phe-

notypes (6), of which phenotype III (brainstem predominant) closely resembles the T1 pattern, whereas phenotypes I and II fit the description of patterns T2 and T3 described in this work. Comparison with the pathology stages as defined by McKee et al. (7) clearly identifies that [F-18]FDDNP PET signal patterns T1–T4 may primarily result from more affected examples of neuropathology stage II and from stages III and IV (Table S2) (7, 11), as they all show prominent neuropathology in medial temporal lobe structures. [F-18]FDDNP PET signal pattern T4 parallels neuropathology of severe stage IV in widespread distribution of signal and in signs of severe atrophy of ventricles. Patterns T2 and T3 would fit into stage III and milder examples of stage IV (Table S2) (7).

[F-18]FDDNP Signal Is Consistent with Mood and Cognitive Disorders in Suspected CTE. Dysfunction within brain circuits, caused by axonal damage leading eventually to PHF-tau aggregate accumulation in CTE, is believed to be the trigger for the mood disorders observed in these subjects who have experienced multiple concussions and subconcussions. Presence of axonal injury in brainstem and cortical white matter has been demonstrated postmortem in teenagers who had a history of playing high school American football (11). Such neurodegenerative processes can produce typical manifestations, initially involving behavioral and mood symptoms and leading to subsequent impairments of cognition and, in some cases, motor impairments in later stages (22).

The [F-18]FDDNP PET results in this work show direct early involvement of brain areas that participate in processing of emotions, mood, and behavior. We observed neuropathology deposition using [F-18]FDDNP PET even in the minimally affected subjects, in the amygdala, several areas of the frontal cortex including the ACG, medial thalamus, hypothalamus, and dorsal midbrain (which contains the periaqueductal gray; Fig. 3). This midbrain pathology distribution pattern has also been reported recently in a retired Australian rugby player with CTE (stage IV) (11). Our [F-18]FDDNP PET imaging results, together with neuropathology observations at autopsy, highlight the selective vulnerability of these midbrain structures, some of which are involved in maintaining consciousness, modulating pain, and controlling defensive behavior (27).

Resting state fMRI studies also have shown that connectivity in these circuits is altered in generalized anxiety disorder (40), panic disorder (41), and depression (42). Some aspects of these neuronal circuits have also been closely connected with other neurodegenerative tauopathies, e.g., progressive supranuclear palsy, as demonstrated by Gardner et al. (43) and further confirmed by direct measurement of PHF-tau accumulation with [F-18]FDDNP PET (19). It has been speculated that in this case, the connectivity of these circuits offers an opportunity for transmissibility of tau aggregation to different brain regions in a predictable manner (44). It is possible that similar relationship between neuropathology accumulation and the pattern of involved neuronal circuits also exists in CTE, and our current observations seem to confirm this possibility.

Regardless of the predictable mechanism of neuropathology transmissibility through the connectivity of these circuits, the present study supports a correlation between the mechanical effects of concussions and subconcussions on specific brain areas and accumulation of neuroaggregates with the subsequent neuronal dysfunction and their corresponding neuropsychiatric consequences. However, effective confirmation awaits a larger cohort of subjects, also including subjects suffering brain concussions that may be biomechanically different from those found in American football players (e.g., war veterans, boxers). Exposure to blasts from explosive devices has caused changes consistent with TBI in war veterans, with clinical signs and changes in their DTI MRI scans consistent with traumatic diffuse axonal injury. Our initial [F-18]FDDNP PET studies in war veterans and other severe TBIs ($n = 8$) seem to indicate that blast-induced

concussions present with a different neuropathology deposition profile than that found in blunt-force TBI or contact-sport-related concussions (Fig. S3).

Clinical diagnosis of CTE remains elusive, and alternative approaches using blood-based biomarkers of cellular degeneration (45) are being explored; however, such methods may provide information about the presence of neurodegenerative processes but not their brain distribution and thus may be inferior to brain imaging biomarkers. DTI MRI (46) can provide useful information about axonal injury in the white matter in CTE but is not specific to this condition as other neurodegenerative diseases (e.g., AD) can have similar patterns of white matter degeneration caused by different mechanisms. Resting state fMRI has also been used to assess changes in large-scale cognitive networks in concussed athletes and in subjects with a history of TBI (47).

The present work suggests that, based on the definition of disease-specific tau pathology deposition stages in suspected CTE, we can use neuropathology deposition as a brain tissue target for PET molecular imaging probes with in vivo sensitivity for these neuroaggregates. However, considering that tau deposits are not specific for CTE but are present in other tauopathies and also in AD, a simple positive or negative reading with PHF-tau PET imaging probes is in itself clinically irrelevant. Only when combined with the regional sensitivity of PET will these probes provide significant in vivo information about regional tau deposition throughout the entire brain, at the earliest possible stage when medical management is most likely to succeed with CTE. This potential can be realized if the molecular imaging probe used has sufficient sensitivity for in vivo detection of relevant neuropathology aggregates and reliably reflects the presence of these aggregates in all brain regions affected in a concentration-dependent manner, in agreement with autopsy determinations and with the prevalent mood and cognitive symptoms observed in this patient population.

Conclusion

This work with [F-18]FDDNP PET offers a sensitive method to visualize and quantify the regional presence of neuroaggregates in the living brain of human subjects with mTBI and suspected CTE and generates useful information about the mechanisms underlying disease staging and the mood disorders observed in these patients. It also offers the potential for early diagnosis of CTE in living subjects, when the probability of successful experimental therapeutic interventions would be greatest. Based on neuropathology indicators (7) (Tables S1 and S2), these [F-18]FDDNP distribution patterns in suspected CTE are largely due to PHF-tau in milder CTE stages (stages I–III), with possible TDP-43 and A β contributions in advanced CTE stages (stage IV) and in CTE with comorbidities. These [F-18]FDDNP topographic distribution patterns are unique among neurodegenerative diseases and significantly different from those found in AD (Figs. 1 and 2), progressive supranuclear palsy (19), and fronto-temporal lobar degeneration (20). Thus, [F-18]FDDNP PET offers critical help in their differential diagnosis within a context of clinical history, physical examination, neuropsychiatric evaluation, and conventional radiological scans. These promising results provide the basis for a larger trial to determine the scope of this imaging procedure for CTE and for the use of this PET imaging technique to monitor disease progression in follow-up studies.

Materials and Methods

Written, informed consent for this [F-18]FDDNP PET imaging study was obtained from subjects in accordance with procedures of the Office of the Human Research Protection Program (OHRPP) of the University of California, Los Angeles, under strict, standard ethics guidelines.

Patient Population and Neurobehavioral Symptoms. The mTBI group included subjects with an increased risk of developing CTE as a result of having re-

ceived repetitive concussions and subconcussions and presenting persistent cognitive, behavioral, and psychiatric problems, as defined by McKee et al. (7). It consisted of 14 retired male professional athletes who played American football professionally with histories of mood and cognitive symptoms as described above and in Table 1. Subjects TBI01–TBI05 from a preliminary report (16) have been included in this work. All mTBI subjects were college-educated retired professional American football players (age range, 40–86 y; mean \pm SD = 57.2 \pm 11.6 y; mean years of education \pm SD = 16.2 \pm 1.4 y), who had played from 9 to 17 combined preprofessional (high school, college) and professional years (mean \pm SD = 13.4 \pm 3.6). All players, with the exception of a 64-y-old former quarterback (TBI02; Table 1), showed evidence of cognitive impairment. A standard neuropsychological test battery indicated that 12 subjects had a diagnosis of mild cognitive impairment (MCI), which is a risk state for dementia. A 73-y-old former offensive guard had a diagnosis of dementia (TBI03). Most subjects also showed symptoms of depression (mean \pm SD: HAM-D score = 12.8 \pm 8.3) and anxiety (mean \pm SD: HAM-A score = 12.1 \pm 8.7). The mTBI subjects also had more prominent cognitive and mood symptoms than motor symptoms. As part of the neurological examinations, motor and balance performance were measured on nine subjects using a modified Balance Error Scoring System (BESS) assessment (mean score \pm SD = 18.9 \pm 5.6) (48) and the Chronic Brain Injury Scale (mean score \pm SD = 2.9 \pm 1.1) (49).

Radiosynthesis. [F-18]FDDNP was prepared as previously described (50) following current US Pharmacopeia 823 requirements for chemistry, manufacture, and control of PET radiopharmaceuticals for human use (51).

PET Scanning. All PET scans of the mTBI group were performed on a Biograph PET/CT camera, except for one subject who was scanned using an ECAT HR+ PET camera (subject TBI01) (both Siemens/CTI), with subjects in the supine position and with the imaging plane parallel to the orbito-meatal line as described previously (18). A bolus of [F-18]FDDNP (320–550 MBq) was injected through an indwelling venous catheter as a bolus i.v. injection following a 10-min attenuation scan. The dynamic data acquisition was started at the time of injection, and the following time frames were collected: 6 \times 30, 4 \times 180, and 10 \times 300 s (total duration: 65 min). All PET scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5-mm FWHM) with scatter correction and measured attenuation correction. The resulting images from the PET/CT camera contained 109 contiguous slices with a plane-to-plane separation of 2.0 mm. Performance of PET scanners (e.g., Biograph, ECAT HR or ECAT EXACT HR+ scanner; Siemens CTI) was tested using the Hoffman brain phantom, and no significant differences between images from the two scanners were observed. All subjects from the AD and CTRL groups were scanned as previously reported (18) and summarized in the *SI Materials and Methods*.

Imaging Data Analysis. Quantification of the [F-18]FDDNP binding data for the mTBI group was performed using the Logan graphical method, with the cerebellar gray matter as the reference region, for time points between 15 and 65 min (52, 53). The relative distribution volume (DVR) parametric images were generated and analyzed with the use of regions of interest (ROIs) drawn bilaterally on the coregistered MRI or CT scans for a number of cortical, limbic, and subcortical areas as defined below. No atrophy correction of the PET data was performed. Partial volume effects result in reduction of the PET signal due to brain atrophy, and if performed, this correction would increase the intensity of the [F-18]FDDNP brain signal even further. Results of [F-18]FDDNP PET data quantification are provided as DVR values (Tables S4–S6) and as Z-scores (Tables S7–S9). DVR values for all ROIs are also provided in cumulative form (as group mean DVR value \pm SD) for 28 cognitively intact control subjects and for 24 AD subjects previously reported (18). These subjects were included in the analysis to provide negative (CTRL group) and positive (AD group) reference points for low and high DVR values in the areas where fibrillar protein aggregates are present in AD (predominantly cortical areas). Both the CTRL and AD groups appear as relatively homogeneous groups based on age and cognitive performance, but the TBI group contains subjects with a range of impairments.

ROIs. ROI sets included subcortical areas [striatum (Str), medial thalamus (Th), hypothalamus (Hypo-Th), dorsal midbrain (Midb-D), ventral midbrain (Midb-V), pons (Pons)], limbic areas of the medial temporal lobe [amygdala (Amygd), hippocampus with parahippocampal gyrus and entorhinal cortex (MTL)], and cortical areas [frontal lobe (F), anterior cingulate gyrus (ACG), parietal lobe (P), posterior cingulate gyrus (PCG), lateral temporal lobe (LTL) and occipital lobe (Occ)]. ROIs were drawn bilaterally on each region, with the exception of the dorsal midbrain (Midb-D), where only one ROI was placed, and striatum (Str), which has been determined as an average of caudate nucleus and putamen.

MRI Scanning. MRI scans were performed for the purpose of anatomical reference to aid the analysis of PET data as described previously (18). T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) MRI volumetric scans, using a 3-T Siemens Allegra MRI scanner, were obtained for nine mTBI subjects (sagittal plane; repetition time, 2,300 ms; echo time, 2.93 ms; 160 slices; slice thickness, 1 mm; skip, 0.5 mm; in-plane voxel size, 1.3 × 1.3 mm; field of view, 256 × 256; flip angle, 8°). Four of the other mTBI subjects received CT scans because they could not tolerate an MRI scan (e.g., because of anxiety, claustrophobia, or metal in the body). One subject (TBI10) was unable to undergo either MRI or CT scans.

Statistical Analysis. Statistical analyses were performed with the use of SAS software (version 9.2). $P < 0.0001$ was considered statistically significant unless otherwise stated. One-way ANOVA with Tukey-Kramer post hoc multiple comparisons was used to test for statistically significant differences in regional [F-18] FDDNP binding (DVR values) among the three groups of subjects. Multivariate ANOVA (MANOVA) was used to determine if a selected pair of regional DVR variables showed significant differences among normal controls and CTs. Spearman rank correlations were computed between regional [F-18]FDDNP binding within the mTBI group to determine their associations, and scatter plots were generated to visualize how regional DVR variables related to one another ($P < 0.05$ was considered statistically significant for this test). Discriminant analysis (DA) (54)

was used to evaluate the performance of classification of subjects with known group memberships (CTRL, mTBI, or AD) based on the selected combinations of various regional [F-18]FDDNP DVR values as predictor variables. Because of a large number of possible combinations of predictor variables for DA, a backward elimination analysis was performed to determine the set of predictor variables that optimally discriminating the three groups (54). All predictor variables were first included, and the least significant variable (F -test, $P > 0.15$) was removed in a stepwise manner. This variable elimination procedure was repeated until no variable could be removed. The resulting reduced DA model functions and their canonical variables were used to assess the degree of overlapping between groups by calculating the percent of correct group classification and the overall classification accuracy, both of which were cross-validated by a leave-one-out method (54).

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Supporting Information

Barrio et al. 10.1073/pnas.1409952112

SI Materials and Methods

Cognitively Normal Control and AD Groups. The CTRL group consisted of 28 subjects without any neurological or neuropsychiatric symptoms, 19 males and 9 females, with ages of 30–84 y (mean \pm SD: 64.3 ± 14.1 y). The AD group consisted of 24 subjects with AD, 12 males and 12 females, with ages of 51–87 y (mean \pm SD: 73.5 ± 9.7 y). Both CTRL and AD group subjects were scanned as a part of a larger study on [F-18]FDDNP PET imaging in aging and AD conducted earlier at UCLA, and their cortical [F-18]FDDNP values were reported previously (1). Their [F-18]FDDNP PET scans were reanalyzed for this study using a more complex set of ROIs as defined in *Materials and Methods* with additional regions that were not part of the previous publication (including ACG in the cortex, amygdala in the limbic medial temporal lobe, and a number of ROIs in subcortical regions). All PET scans of the CTRL and AD groups were performed at the UCLA Ahmanson Biomedical Imaging Center PET with the ECAT HR or ECAT EXACT HR+ scanner (Siemens CTI), with subjects in the supine position and with the imaging plane parallel to the orbito-meatal line. A bolus of FDDNP (320–550 MBq) was injected through an indwelling venous catheter, and consecutive dynamic PET scans were ob-

tained for 2 h. Scans were corrected for decay and reconstructed with the use of filtered back-projection (Hann filter, 5.5-mm full width at half maximum), with correction for scatter and measured attenuation. The resulting images contained either 47 contiguous slices with a plane separation of 3.37 mm (with the ECAT HR) or 63 contiguous slices with a plane separation of 2.42 mm (with the EXACT HR+). Imaging results did not differ significantly with the scanner used.

Subjects from the AD group met the standard diagnostic criteria of memory impairment, impairment in at least one other cognitive domain, gradual onset and progressive decline, and impaired occupational or social functioning or both (2, 3). Control subjects had normal cognitive functioning for their age and did not meet the criteria for mild cognitive impairment (4) or AD.

Subjects from the CTRL and AD groups who received an MRI scan were scanned on a 1.5-T (Signa) or 3T (General Electric or Siemens) scanner. For each of these subjects, 54 transverse planes were collected throughout the brain, superior to the cerebellum, with the use of a double-echo, fast spin-echo series with a 24-cm field of view and 256×256 matrix and 3-mm slices with no gap [repetition time, 6,000 (3 T) or 2,000 (1.5 T); echo time, 17/85 (3 T) or 30/90 (1.5 T)] (1).

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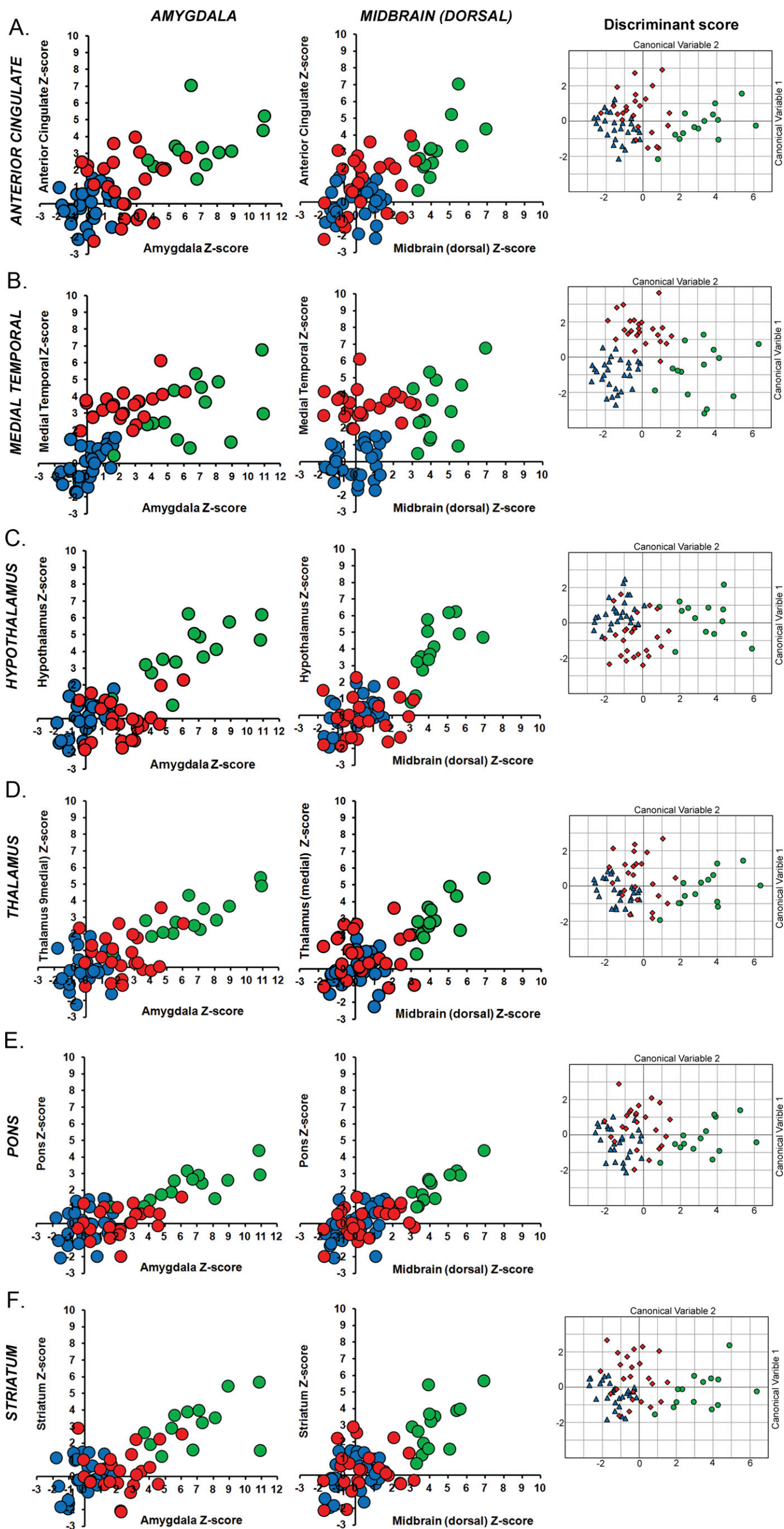


Fig. S1. Correlations of the core regions, amygdala (A–F, Left), and dorsal midbrain (A–F, Center) show that these two regions efficiently separate the mTBI group (green circles) from the AD group (red circles) and CTRL group (blue circles) in several cortical and limbic temporal lobe areas [anterior cingulate gyrus (A), medial temporal lobe (B), hypothalamus (C), thalamus (D), pons (E), and striatum (F)]. [F-18]FDDNP binding is expressed as Z-scores in reference to CTRL group (Tables S7–S9), all values higher than $Z = 2$ are considered significantly higher than the CTRL group values. (A–F, Right) Results of discriminant analysis for each region. Note that in subcortical regions AD and CTRL groups show no separation.

CHRONIC TRAUMATIC ENCEPHALOPATHY

MACROSCOPIC tau immunohistochemistry

MICROSCOPIC tau immunohistochemistry

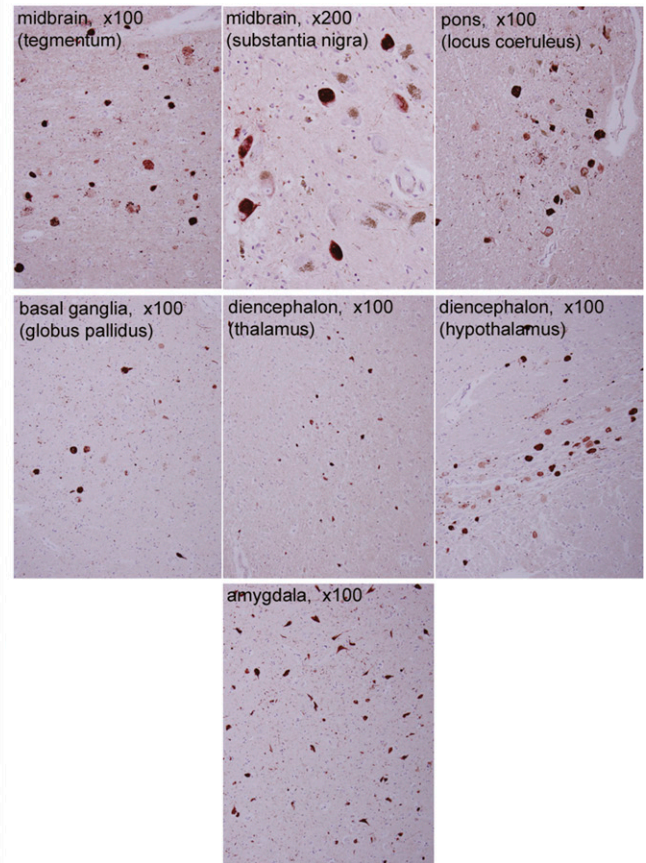
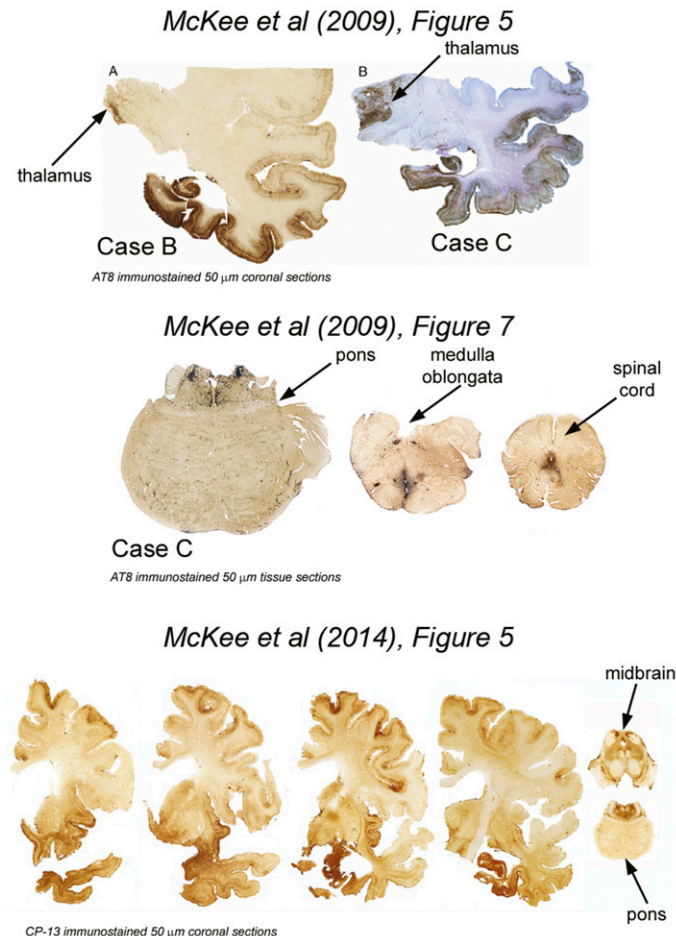


Fig. S2. CTE related hyperphosphorylated tau pathology distribution in subcortical brain regions. (*Left*) Examples of hyperphosphorylated tau immunohistochemistry (IHC) on brain tissue samples from CTE cases published in papers by McKee's group clearly show involvement of basal ganglia and diencephalon in stage IV as shown in refs. 1 and 2. The top and middle sections of the left panel show two cases of pathologically confirmed CTE with more advanced distribution of cortical pathology labeled as cases B and C in ref. 2: large coronally cut tissue sections of cases B and C clearly demonstrate tau IHC in thalamic region at variable levels in the upper section (figure 5 in ref. 2) and the middle section shows dense tau IHC in parts of pons, medulla oblongata, and spinal cord of case C (figure 7 in ref. 2); the bottom section shows a case of Australian rugby player with stage IV CTE with variable levels of tau IHC labeling throughout the cortex, basal ganglia, diencephalon, midbrain, and pons regions (figure 5 in ref. 1). Tissue samples from cases B and C (top and middle section, fully described in ref. 2) were independently analyzed as a part of analysis of neurochemical profile of dementia pugilistica (3), confirming McKee's observation. (*Right*) Additional evidence of the presence of tau deposits in subcortical structures of confirmed CTE is provided by tau IHC in microscopy slides performed on tissues samples from an 80-y-old retired NFL player from the CTE brain collection of Dr. Omalu. Different areas of midbrain (tegmentum, substantia nigra), pons (locus coeruleus), diencephalon (thalamus, hypothalamus), basal ganglia (globus pallidus), and amygdala clearly show presence of tau IHC positive aggregates. [Top and Middle, reproduced with permission from Wolters Kluwer Health; Bottom, reproduced with permission from Springer Science and Business Media.]

1. McKee AC, Daneshvar DH, Alvarez VE, Stein TD (2014) The neuropathology of sport. *Acta Neuropathol* 127(1):29–51.
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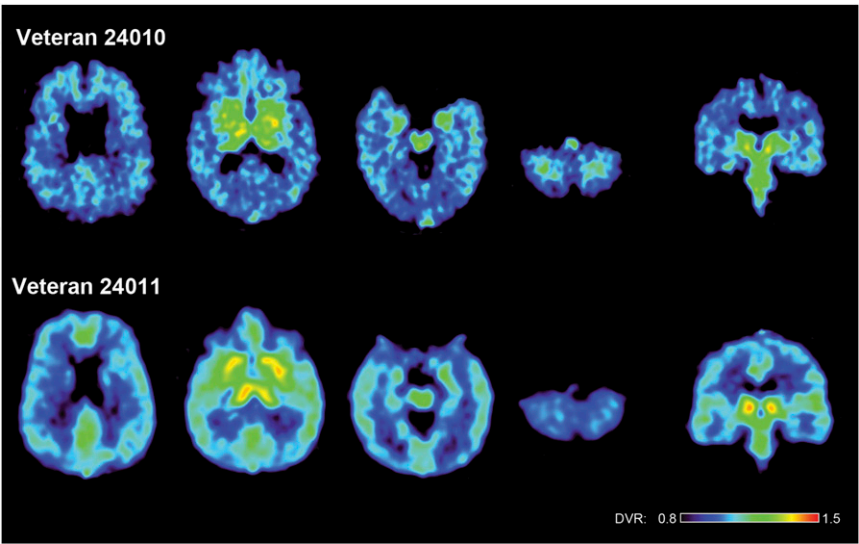


Fig. S3. [F-18]FDDNP DVR parametric images of the brains of two war veterans with the history of multiple blast concussions (mTBIs) during their war zone deployment. The upper row shows a 48-y-old male (veteran 24010) and the lower row a 36-y-old male (veteran 24011). Left four images in each row show transaxial brain images from top of the brain to the bottom. The right image shows a coronal cut through the midbrain. Note different [F-18]FDDNP signal distribution from the patterns T1–T4 described for retired professional American football players (Fig. 1) and a pattern of lower signal in midbrain and amygdala.

Table S1. Pathology distribution in CTE (1)

CTE	Hyperphosphorylated tau	TDP-43	β-Amyloid
Stage I	Focal perivascular NFTs at depth of cortical sulci	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	None
Stage II	NFTs adjacent to focal epicenters, Nucleus basalis of Meynert, Locus coeruleus	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	2 out of 14 cases
Stage III	Dense: medial temporal lobes; Widespread: cortex, diencephalon, brainstem, and spinal cord	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	3 out of 15 cases
Stage IV	Dense and widespread throughout the brain including white matter	Severe intraneuronal and intragial inclusions in cortex, white matter, diencephalon, basal ganglia, brainstem	9 out of 15 cases; as diffuse and neuritic plaques or vascular amyloid - but less than what required for AD diagnosis

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1. McKee AC, et al. (2013) The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136(Pt 1):43–64.

Table S2. Comparison of tau pathology in CTE and AD (1)

Hyperphosphorylated tau pathology	CTE	AD
Mild pathology	CTE stages I–II: NFTs in focal epicentres in cerebral cortex, usually frontal lobe	Braak NFT stages I–III: NFTs in entorhinal cortex, hippocampus and amygdala
Advanced pathology	CTE stages III–IV: High density of NFTs in widespread cortical areas and medial temporal lobe, patchy irregular distribution	Braak NFT stages IV–VI: High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution
Cortical		
Subcortical	High densities of NFTs in thalamus, hypothalamus, mamillary bodies, brainstem; Moderate densities of NFTs in basal ganglia, especially nucleus accumbens	Low densities of NFTs in basal ganglia and brainstem, none in mamillary bodies
White matter	Prominent pathology	Relatively uninvolved

© Oxford University Press (brain.oxfordjournals.org/content/136/1/43).1. McKee AC, et al. (2013) The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136(Pt 1):43–64.**Table S3. Significance of Spearman's rank correlations for ROI combinations within the mTBI group**

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
Amygd	—													
MTL	NS	—												
Midb-V	NS	NS	—											
Midb-D	$P < 0.01$	NS	NS	—										
Hypo-Th	NS	NS	$P < 0.01$	$P < 0.01$	—									
Th	$P < 0.001$	NS	$P < 0.05$	$P < 0.01$	$P < 0.01$	—								
Pons	$P < 0.01$	NS	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.01$	—							
Str	$P < 0.05$	NS	$P < 0.05$	$P < 0.05$	NS	$P < 0.05$	NS	—						
F	$P < 0.001$	NS	NS	$P < 0.001$	NS	NS	$P < 0.05$	NS	—					
ACG	$P < 0.05$	NS	$P < 0.05$	$P < 0.05$	NS	$P < 0.05$	$P < 0.01$	NS	$P < 0.001$	—				
P	$P < 0.05$	NS	NS	$P < 0.01$	$P < 0.01$	NS	$P < 0.05$	NS	$P < 0.001$	$P < 0.05$	—			
PCG	NS	NS	NS	$P < 0.05$	NS	NS	NS	NS	$P < 0.001$	$P < 0.001$	$P < 0.01$	—		
LTL	$P < 0.05$	NS	NS	$P < 0.001$	NS	$P < 0.05$	$P < 0.001$	NS	$P < 0.01$	$P < 0.05$	$P < 0.001$	$P < 0.01$	—	
OCC	NS	NS	NS	NS	NS	NS	NS	NS	$P < 0.01$	$P < 0.001$	NS	$P < 0.05$	NS	—

Areas shaded in orange and green show significant correlations of limbic medial temporal lobe areas with subcortical (orange) and cortical (green) regions. Areas shaded in blue show significant correlations of subcortical areas with cortical areas. Significant cortico-cortical and subcortico-subcortical correlations are highlighted in purple and yellow, respectively. NS, not significant ($P > 0.05$).

Table S4. mTBI group [F-18]FDDNP DVR values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
TBI01	1.553	1.265	1.478	1.517	1.465	1.713	1.476	1.716	1.167	1.282	1.119	1.271	1.168	1.088
TBI02	1.356	1.211	1.269	1.304	1.274	1.425	1.287	1.525	1.132	1.241	1.080	1.120	1.098	1.012
TBI03	1.483	1.141	1.433	1.352	1.517	1.564	1.341	1.700	1.109	1.228	1.114	1.092	1.097	0.923
TBI04	1.454	1.222	1.244	1.372	1.437	1.495	1.258	1.568	1.170	1.225	1.121	1.158	1.113	0.986
TBI05	1.333	1.168	1.375	1.333	1.409	1.430	1.277	1.408	1.110	1.184	1.108	1.129	1.111	0.963
TBI06	1.392	1.133	1.421	1.436	1.541	1.623	1.385	1.592	1.244	1.397	1.176	1.305	1.189	1.110
TBI07	1.425	1.196	1.245	1.359	1.415	1.552	1.327	1.546	1.132	1.194	1.080	1.206	1.132	0.978
TBI08	1.417	1.215	1.402	1.447	1.475	1.447	1.364	1.598	1.215	1.238	1.154	1.158	1.189	1.011
TBI09	1.556	1.179	1.387	1.416	1.539	1.669	1.365	1.433	1.198	1.319	1.149	1.288	1.201	1.008
TBI10	1.308	1.167	1.172	1.338	1.369	1.410	1.252	1.457	1.129	1.189	1.067	1.110	1.097	0.986
TBI11	1.404	1.233	1.286	1.353	1.483	1.467	1.346	1.433	1.082	1.157	1.056	1.083	1.118	0.955
TBI12	1.295	1.165	1.285	1.321	1.393	1.491	1.224	1.506	1.106	1.206	1.014	1.095	1.044	1.004
TBI13	1.363	1.144	1.361	1.356	1.400	1.485	1.339	1.578	1.142	1.232	1.043	1.100	1.080	0.979
TBI14	1.220	1.123	1.257	1.318	1.292	1.327	1.220	1.371	1.082	1.124	1.056	1.118	1.077	0.951

Table S5. CTRL group [F-18]FDDNP DVR values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
CTRL01	1.155	1.095	1.180	1.122	1.169	1.238	1.161	1.425	1.025	1.108	1.016	1.107	1.038	0.961
CTRL02	1.124	1.145	1.179	1.162	1.300	1.233	1.193	1.210	1.005	1.064	1.052	1.126	1.054	0.948
CTRL03	1.143	1.087	1.081	1.190	1.274	1.290	1.239	1.307	1.025	1.082	1.083	1.078	1.045	1.091
CTRL04	1.135	1.074	1.081	1.141	1.331	1.403	1.149	1.421	1.045	1.118	1.042	1.076	1.047	0.983
CTRL05	1.157	1.116	1.204	1.077	1.152	1.195	1.094	1.277	1.015	1.033	1.078	1.152	1.065	1.057
CTRL06	1.138	1.073	1.165	1.193	1.240	1.058	1.194	1.390	1.056	1.002	1.007	1.016	1.046	1.005
CTRL07	1.213	1.107	1.160	1.195	1.229	1.302	1.105	1.342	1.033	1.033	1.024	1.109	1.046	0.997
CTRL08	1.170	1.123	1.080	1.088	1.214	1.410	1.257	1.423	1.059	1.159	1.033	1.040	1.079	1.014
CTRL09	1.209	1.146	1.201	1.223	1.229	1.242	1.257	1.339	1.049	1.102	1.078	1.071	1.032	0.998
CTRL10	1.096	1.095	1.140	1.139	1.222	1.350	1.173	1.399	1.123	1.136	1.068	1.074	1.072	1.051
CTRL11	1.142	1.094	1.198	1.208	1.271	1.367	1.250	1.394	1.024	1.090	1.026	1.040	1.022	0.995
CTRL12	1.162	1.081	1.136	1.142	1.204	1.277	1.147	1.277	0.978	1.014	1.017	1.088	1.058	0.955
CTRL13	1.167	1.135	1.140	1.151	1.242	1.192	1.125	1.257	1.060	1.142	1.092	1.100	1.107	0.974
CTRL14	1.205	1.138	1.135	1.162	1.260	1.315	1.260	1.417	1.073	1.146	1.070	1.085	1.071	0.985
CTRL15	1.185	1.132	1.046	1.078	1.271	1.241	1.078	1.311	1.055	1.149	1.092	1.155	1.058	1.084
CTRL16	1.189	1.122	1.096	1.195	1.269	1.225	0.997	1.287	1.043	1.153	1.074	1.114	1.076	1.107
CTRL17	1.218	1.137	1.156	1.206	1.244	1.115	1.140	1.308	1.069	1.111	1.044	1.127	1.074	1.020
CTRL18	1.123	1.102	1.067	1.061	1.141	1.123	1.048	1.188	1.005	1.075	1.092	1.097	1.068	1.072
CTRL19	1.167	1.094	1.218	1.150	1.224	1.241	1.114	1.362	1.074	1.099	1.057	1.087	1.060	0.987
CTRL20	1.147	1.136	1.145	1.064	1.227	1.222	1.056	1.309	1.066	1.119	1.062	1.061	1.022	1.031
CTRL21	1.172	1.118	1.195	1.183	1.227	1.337	1.222	1.300	1.071	1.130	1.033	1.097	1.082	0.982
CTRL22	1.102	1.101	1.039	1.096	1.163	1.170	1.069	1.282	0.996	1.090	1.025	1.035	1.066	0.998
CTRL23	1.122	1.105	1.056	1.046	1.174	1.163	1.102	1.224	0.988	1.042	1.059	0.984	1.102	0.998
CTRL24	1.106	1.084	1.051	1.072	1.169	1.193	0.990	1.197	1.038	1.076	1.027	1.116	1.023	0.979
CTRL25	1.205	1.131	1.151	1.169	1.242	1.339	1.151	1.355	1.072	1.119	1.077	1.052	1.102	1.051
CTRL26	1.224	1.147	1.236	1.195	1.321	1.296	1.195	1.327	1.047	1.098	1.093	1.055	1.059	1.074
CTRL27	1.173	1.102	1.108	1.066	1.277	1.226	1.146	1.306	1.009	1.057	1.051	1.042	1.097	1.111
CTRL28	1.177	1.112	1.138	1.079	1.269	1.231	1.144	1.368	0.999	1.069	1.036	1.115	1.115	1.072

Table S6. AD group [F-18]FDDNP DVR values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
AD01	1.159	1.194	1.108	1.234	1.157	1.154	1.236	1.321	1.126	1.192	1.121	1.165	1.201	1.092
AD02	1.380	1.209	1.196	1.140	1.348	1.477	1.267	1.500	1.148	1.213	1.172	1.175	1.179	1.039
AD03	1.288	1.176	1.123	1.155	1.215	1.241	1.190	1.343	1.108	1.158	1.143	1.193	1.122	1.019
AD04	1.242	1.180	1.130	1.111	1.168	1.190	1.116	1.179	1.137	1.055	1.153	1.162	1.138	1.053
AD05	1.235	1.174	1.156	1.103	1.219	1.477	1.220	1.294	1.096	1.029	1.191	1.209	1.175	1.068
AD06	1.308	1.200	1.078	1.094	1.236	1.235	1.202	1.361	1.112	1.045	1.173	1.203	1.143	1.035
AD07	1.173	1.176	1.085	1.143	1.165	1.332	1.065	1.301	1.123	1.144	1.177	1.181	1.140	1.224
AD08	1.205	1.199	1.188	1.270	1.288	1.402	1.222	1.288	1.108	1.137	1.097	1.182	1.159	0.981
AD09	1.220	1.192	1.196	1.118	1.237	1.346	1.096	1.371	1.075	1.125	1.136	1.156	1.163	1.065
AD10	1.173	1.174	1.071	1.042	1.309	1.365	1.120	1.298	1.101	0.999	1.146	1.200	1.118	1.084
AD11	1.196	1.185	1.090	1.207	1.263	1.304	1.198	1.353	1.113	1.183	1.168	1.143	1.171	1.110
AD12	1.159	1.198	1.069	1.097	1.144	1.276	1.149	1.392	1.052	1.179	1.128	1.166	1.151	1.034
AD13	1.217	1.190	1.280	1.311	1.282	1.168	1.129	1.301	1.085	1.200	1.184	1.184	1.124	1.075
AD14	1.271	1.164	1.162	1.271	1.170	1.274	1.240	1.287	1.094	1.054	1.146	1.161	1.128	1.061
AD15	1.277	1.196	1.145	1.227	1.206	1.277	1.190	1.331	1.077	1.065	1.068	1.213	1.135	1.119
AD16	1.243	1.207	1.089	1.043	1.148	1.159	0.997	1.174	1.115	1.092	1.150	1.204	1.146	1.095
AD17	1.326	1.251	1.134	1.147	1.218	1.257	1.138	1.290	1.108	1.185	1.109	1.170	1.203	1.083
AD18	1.239	1.179	1.138	1.149	1.260	1.261	1.095	1.345	1.096	1.094	1.119	1.137	1.151	0.973
AD19	1.276	1.196	1.034	1.084	1.228	1.403	1.188	1.477	1.142	1.227	1.166	1.168	1.188	1.006
AD20	1.218	1.189	1.126	1.177	1.219	1.280	1.080	1.393	1.104	1.249	1.157	1.162	1.151	1.116
AD21	1.264	1.157	1.102	1.126	1.171	1.330	1.151	1.255	1.108	1.120	1.154	1.167	1.154	1.038
AD22	1.330	1.206	1.264	1.251	1.332	1.559	1.190	1.477	1.142	1.181	1.147	1.192	1.173	0.951
AD23	1.146	1.157	1.103	1.131	1.289	1.454	1.126	1.523	1.163	1.200	1.195	1.208	1.165	1.051
AD24	1.267	1.192	1.215	1.296	1.233	1.422	1.150	1.414	1.163	1.264	1.151	1.215	1.137	1.046

Table S7. mTBI group Z-score values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
TBI01	10.824	6.782	6.069	6.903	4.702	5.420	4.400	5.704	3.885	4.372	2.443	4.711	4.053	1.412
TBI02	5.381	4.379	2.363	3.032	0.814	2.044	1.892	2.941	2.815	3.427	0.966	0.953	1.322	-0.179
TBI03	8.885	1.304	5.276	3.901	5.769	3.678	2.599	5.466	2.133	3.138	2.264	0.247	1.294	-2.057
TBI04	8.097	4.882	1.927	4.271	4.130	2.872	1.508	3.562	3.978	3.058	2.547	1.902	1.931	-0.728
TBI05	4.747	2.484	4.251	3.558	3.552	2.104	1.752	1.246	2.143	2.107	2.044	1.177	1.824	-1.202
TBI06	6.364	0.945	5.066	5.438	6.251	4.358	3.193	3.910	6.227	7.054	4.606	5.552	4.874	1.865
TBI07	7.287	3.698	1.946	4.038	3.678	3.530	2.421	3.251	2.837	2.348	0.988	3.102	2.659	-0.902
TBI08	7.060	4.576	4.725	5.631	4.898	2.303	2.911	4.001	5.370	3.360	3.766	1.901	4.882	-0.197
TBI09	10.903	2.984	4.455	5.060	6.201	4.901	2.926	1.608	4.851	5.236	3.593	5.150	5.322	-0.267
TBI10	4.049	2.422	0.655	3.656	2.738	1.869	1.423	1.962	2.732	2.218	0.484	0.687	1.294	-0.726
TBI11	6.719	5.366	2.665	3.925	5.066	2.539	2.664	1.609	1.313	1.479	0.060	0.019	2.105	-1.371
TBI12	3.690	2.356	2.652	3.342	3.233	2.819	1.046	2.672	2.031	2.611	-1.501	0.313	-0.779	-0.352
TBI13	5.575	1.440	4.000	3.981	3.371	2.745	2.574	3.710	3.137	3.217	-0.398	0.453	0.644	-0.874
TBI14	1.615	0.497	2.159	3.285	1.183	0.903	1.004	0.717	1.304	0.701	0.091	0.893	0.500	-1.460

Z-score defined as $(DVR_{(mTBI-ROI)} - DVR_{(CTRLgroup-mean)}) / SD_{(CTRLgroup)}$; CTRL group DVR mean values and SDs for each ROI are provided in the Table 2.

Table S8. CTRL group Z-score values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
CTRL01	-0.194	-0.755	0.791	-0.286	-1.324	-0.139	0.218	1.493	-0.433	0.331	-1.421	0.623	-1.002	-1.246
CTRL02	-1.048	1.460	0.778	0.445	1.352	-0.192	0.639	-1.607	-1.050	-0.685	-0.086	1.104	-0.374	-1.517
CTRL03	-0.505	-1.099	-0.958	0.954	0.813	0.474	1.246	-0.209	-0.447	-0.263	1.085	-0.092	-0.744	1.483
CTRL04	-0.728	-1.667	-0.965	0.064	1.980	1.793	0.050	1.440	0.170	0.574	-0.451	-0.164	-0.641	-0.793
CTRL05	-0.137	0.175	1.220	-1.095	-1.669	-0.639	-0.673	-0.649	-0.727	-1.399	0.898	1.755	0.043	0.751
CTRL06	-0.646	-1.713	0.523	1.009	0.112	-2.248	0.658	0.996	0.494	-2.125	-1.755	-1.657	-0.703	-0.323
CTRL07	1.432	-0.231	0.441	1.049	-0.094	0.615	-0.535	0.295	-0.197	-1.402	-1.139	0.665	-0.668	-0.504
CTRL08	0.233	0.502	-0.981	-0.912	-0.414	1.872	1.483	1.465	0.592	1.528	-0.781	-1.049	0.591	-0.144
CTRL09	1.307	1.500	1.173	1.551	-0.107	-0.093	1.493	0.246	0.307	0.191	0.923	-0.269	-1.223	-0.482
CTRL10	-1.816	-0.728	0.093	0.026	-0.242	1.170	0.370	1.123	2.560	0.984	0.525	-0.200	0.323	0.640
CTRL11	-0.542	-0.777	1.120	1.281	0.750	1.375	1.396	1.049	-0.478	-0.077	-1.046	-1.053	-1.627	-0.544
CTRL12	0.016	-1.379	0.016	0.084	-0.622	0.322	0.032	-0.638	-1.868	-1.856	-1.395	0.145	-0.235	-1.372
CTRL13	0.144	1.007	0.088	0.250	0.166	-0.671	-0.269	-0.926	0.617	1.122	1.444	0.440	1.690	-0.988
CTRL14	1.185	1.148	0.000	0.447	0.532	0.763	1.532	1.386	1.024	1.221	0.599	0.063	0.267	-0.741
CTRL15	0.645	0.879	-1.570	-1.093	0.747	-0.106	-0.885	-0.155	0.489	1.302	1.425	1.821	-0.238	1.330
CTRL16	0.756	0.458	-0.684	1.046	0.714	-0.290	-1.956	-0.499	0.110	1.377	0.755	0.786	0.495	1.814
CTRL17	1.557	1.108	0.366	1.250	0.199	-1.572	-0.066	-0.202	0.907	0.412	-0.362	1.123	0.383	-0.020
CTRL18	-1.076	-0.437	-1.198	-1.390	-1.900	-1.483	-1.286	-1.932	-1.034	-0.424	1.443	0.373	0.159	1.068
CTRL19	0.159	-0.781	1.467	0.227	-0.206	-0.102	-0.403	0.584	1.064	0.126	0.116	0.119	-0.160	-0.709
CTRL20	-0.396	1.073	0.170	-1.338	-0.145	-0.331	-1.183	-0.174	0.810	0.600	0.319	-0.515	-1.631	0.210
CTRL21	0.280	0.275	1.053	0.823	-0.138	1.018	1.018	-0.304	0.969	0.849	-0.781	0.363	0.691	-0.804
CTRL22	-1.652	-0.489	-1.702	-0.752	-1.445	-0.934	-1.004	-0.573	-1.326	-0.079	-1.077	-1.176	0.077	-0.474
CTRL23	-1.091	-0.295	-1.397	-1.668	-1.231	-1.013	-0.571	-1.410	-1.560	-1.188	0.179	-2.452	1.501	-0.481
CTRL24	-1.548	-1.234	-1.489	-1.197	-1.320	-0.663	-2.057	-1.805	-0.040	-0.414	-1.000	0.838	-1.578	-0.876
CTRL25	1.192	0.868	0.280	0.563	0.153	1.043	0.082	0.478	0.995	0.601	0.870	-0.760	1.489	0.628
CTRL26	1.718	1.546	1.788	1.043	1.764	0.534	0.666	0.080	0.233	0.111	1.492	-0.671	-0.200	1.113
CTRL27	0.320	-0.436	-0.474	-1.306	0.865	-0.285	0.019	-0.226	-0.934	-0.849	-0.099	-0.991	1.306	1.901
CTRL28	0.437	0.022	0.053	-1.073	0.711	-0.219	-0.013	0.672	-1.244	-0.568	-0.679	0.831	2.005	1.081

Z-score defined as $(DVR_{(CTRL-ROI)} - DVR_{(CTRLgroup-mean)})/SD_{(CTRLgroup)}$; CTRL group DVR mean values and SDs for each ROI are provided in the Table 2.

Table S9. AD group Z-score values

	Amygd	MTL	Midb-V	Midb-D	Hypo-Th	Th	Pons	Str	F	ACG	P	PCG	LTL	Occ
AD01	-0.070	3.644	-0.486	1.760	-1.571	-1.126	1.215	-0.005	2.643	2.298	2.540	2.062	5.327	1.495
AD02	6.054	4.312	1.086	0.048	2.312	2.650	1.616	2.572	3.314	2.771	4.440	2.314	4.495	0.383
AD03	3.508	2.814	-0.216	0.312	-0.385	-0.101	0.593	0.318	2.098	1.492	3.375	2.777	2.250	-0.046
AD04	2.230	3.008	-0.088	-0.490	-1.345	-0.699	-0.383	-2.060	2.979	-0.904	3.754	2.004	2.885	0.669
AD05	2.026	2.727	0.373	-0.633	-0.317	2.658	1.002	-0.398	1.737	-1.492	5.166	3.166	4.309	0.985
AD06	4.041	3.882	-1.013	-0.795	0.048	-0.179	0.762	0.574	2.208	-1.130	4.501	3.030	3.086	0.309
AD07	0.324	2.815	-0.888	0.103	-1.405	0.960	-1.054	-0.299	2.565	1.171	4.641	2.463	2.956	4.267
AD08	1.193	3.866	0.944	2.406	1.107	1.774	1.021	-0.487	2.092	1.015	1.607	2.503	3.713	-0.828
AD09	1.618	3.536	1.085	-0.355	0.049	1.126	-0.651	0.721	1.100	0.735	3.082	1.835	3.849	0.929
AD10	0.321	2.766	-1.138	-1.743	1.523	1.344	-0.335	-0.335	1.868	-2.207	3.484	2.943	2.114	1.337
AD11	0.941	3.219	-0.800	1.261	0.591	0.633	0.707	0.457	2.242	2.088	4.323	1.514	4.148	1.876
AD12	-0.086	3.806	-1.172	-0.745	-1.834	0.307	0.053	1.015	0.381	1.997	2.781	2.096	3.397	0.286
AD13	1.525	3.441	2.556	3.156	0.984	-0.955	-0.214	-0.294	1.390	2.477	4.910	2.541	2.344	1.144
AD14	3.013	2.315	0.468	2.419	-1.297	0.281	1.258	-0.498	1.666	-0.921	3.465	1.972	2.499	0.844
AD15	3.202	3.726	0.174	1.632	-0.569	0.318	0.595	0.132	1.143	-0.661	0.542	3.279	2.786	2.061
AD16	2.245	4.217	-0.810	-1.724	-1.746	-1.067	-1.969	-2.127	2.320	-0.029	3.632	3.037	3.203	1.566
AD17	4.557	6.143	-0.016	0.171	-0.326	0.080	-0.097	-0.454	2.098	2.125	2.092	2.183	5.415	1.304
AD18	2.151	2.967	0.056	0.204	0.519	0.129	-0.660	0.344	1.718	0.017	2.464	1.375	3.397	-0.992
AD19	3.166	3.735	-1.790	-0.983	-0.131	1.792	0.567	2.245	3.124	3.095	4.218	2.132	4.814	-0.305
AD20	1.566	3.415	-0.155	0.716	-0.303	0.348	-0.860	1.031	1.966	3.607	3.900	1.984	3.405	2.000
AD21	2.829	2.012	-0.581	-0.215	-1.293	0.939	0.079	-0.955	2.086	0.628	3.775	2.130	3.492	0.352
AD22	4.656	4.147	2.275	2.063	1.993	3.612	0.594	2.253	3.133	2.024	3.508	2.750	4.227	-1.467
AD23	-0.435	1.977	-0.570	-0.126	1.108	2.389	-0.249	2.918	3.778	2.489	5.329	3.132	3.949	0.633
AD24	2.901	3.540	1.414	2.875	-0.032	2.015	0.072	1.336	3.761	3.964	3.645	3.327	2.849	0.535

Z-score defined as $(DVR_{(AD-ROI)} - DVR_{(CTRLgroup-mean)})/SD_{(CTRLgroup)}$; CTRL group DVR mean values and SDs for each ROI are provided in the Table 2.

BAILES

EXHIBIT 20

Why do People Avoid Medical Care? A Qualitative Study Using National Data

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BACKGROUND: Many studies have examined barriers to health care utilization, with the majority conducted in the context of specific populations and diseases. Less research has focused on why people avoid seeking medical care, even when they suspect they should go.

OBJECTIVE: The purpose of the study was to present a comprehensive description and conceptual categorization of reasons people avoid medical care.

DESIGN: Data were collected as part of the 2008 Health Information National Trends Survey, a cross-sectional national survey.

PARTICIPANTS: Participant-generated reasons for avoiding medical care were provided by 1,369 participants (40% male; $M_{age}=48.9$; 75.1% non-Hispanic white, 7.4% non-Hispanic black, 8.5% Hispanic or Latino/a).

MAIN MEASURES: Participants first indicated their level of agreement with three specific reasons for avoiding medical care; these data are reported elsewhere. We report responses to a follow-up question in which participants identified other reasons they avoid seeking medical care. Reasons were coded using a general inductive approach.

KEY RESULTS: Three main categories of reasons for avoiding medical care were identified. First, over one-third of participants (33.3% of 1,369) reported unfavorable evaluations of seeking medical care, such as factors related to physicians, health care organizations, and affective concerns. Second, a subset of participants reported low perceived need to seek medical care (12.2%), often because they expected their illness or symptoms to improve over time (4.0%). Third, many participants reported traditional barriers to medical care (58.4%), such as high cost (24.1%), no health insurance (8.3%), and time constraints (15.6%). We developed a conceptual model of medical care avoidance based on these results.

CONCLUSIONS: Reasons for avoiding medical care were nuanced and highly varied. Understanding why people do not make it through the clinic door is critical to extending the reach and effectiveness of patient care, and these data point to new directions for research and strategies to reduce avoidance.

KEYWORDS: Medical care avoidance; Health care barriers; Health care utilization; Qualitative.

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INTRODUCTION

People often avoid seeking medical care even when they suspect it may be necessary;^{1–4} nearly one-third of respondents in a recent national United States (U.S.) survey reported avoiding the doctor.^{5–7} Even individuals with major health problems^{4,8,9} or who are experiencing symptoms^{10–12} avoid seeking medical care. For example, in one study, 17% of patients diagnosed with rectal tumors reported that they waited a year or more to seek medical consultation after noticing symptoms, with some waiting up to five years.¹² Avoiding medical care may result in late detection of disease, reduced survival, and potentially preventable human suffering.^{1,8,13,14}

In the present study, we sought to understand why people avoid seeking medical care. Avoidance of medical care has been defined as “keeping away from something [in a medical context] that is thought to cause mental or physical distress.”⁸ Avoidance can also occur as a result of barriers, which can be defined as factors that limit access to or ease of obtaining quality health care (e.g., financial concerns, time constraints).^{1,15} Avoidance of medical care can occur at any point on the disease continuum, including preventing and detecting asymptomatic disease, noticing symptoms and interpreting their significance, seeking care after determining a potential need, and complying with recommended treatment.^{1,2,16} Of note, the term “patient delay” has also been used to describe phenomena related to avoidance, but guidelines for research on early cancer diagnosis have suggested instead using the more informative terms “appraisal interval” (the time taken to interpret symptoms) and “help-seeking interval” (the time taken to seek care after determining a need).¹⁷

To date, research on avoidance of medical care has been limited in the extent to which it examines the broad spectrum of reasons for avoidance (but see⁷), often focusing on specific factors such as barriers or psychological characteristics (e.g., lack of insurance, fear of a diagnosis).^{4–6,15,18–24} A conceptual review of reasons people avoid medical care identified only six qualitative or mixed-methods studies assessing participant-generated reasons, all of which used convenience samples with predominately white participants.¹ Moreover, five of the six studies reviewed assessed avoidance of specific

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procedures.¹ The exception was a focus group study among a sample of Hispanics that explored reasons for avoiding medical visits in response to warning signs of heart disease, cancer, and diabetes.¹¹ This qualitative study identified factors such as low trust in doctors, low perceived severity of symptoms, emotional factors (e.g., denial, avoiding worry, embarrassment), practical barriers, and prior negative experiences as contributing to avoidance.¹¹

Given the significance and prevalence of medical care avoidance in the U.S.,^{1,5} there is a need for continued basic qualitative research that can uncover the reasons underlying this phenomenon. Simply put, why do people avoid medical visits that could save lives or reduce suffering, whether through early detection of disease or timely treatment? To help answer this question, the present study used data collected from a large national sample. The purpose of the study was to identify the reasons people avoid seeking medical care and to classify these reasons into conceptually distinct categories reflecting underlying factors contributing to avoidance. Ultimately, we sought to develop a model of medical care avoidance that can inform efforts to promote care-seeking, help providers reduce avoidance in their patient populations, and promote theoretical advancement in this area of research.

METHODS

Data Source

Data were obtained from the National Cancer Institute's 2008 Health Information National Trends Survey (HINTS). This cross-sectional survey collects data from a nationally representative sample of civilian non-institutionalized adults aged 18 and over in order to assess trends and patterns in health communication. Data were collected from January through April 2008. Phone and mail surveys were administered to maximize response rates (24.2 and 31.0 %, respectively). The survey was completed by 7,674 participants. Details of the study design have been published elsewhere.²⁵⁻²⁷

Measures

Participants were first asked whether they "avoid visiting their doctor even when they suspect they should." Participants who responded "yes" ($n=2,327$) were then asked to what extent they endorsed three researcher-identified reasons for avoiding the doctor (i.e., feeling uncomfortable when their body is being examined, fear of having a serious illness, and because it makes them think of dying); results concerning these items have been published elsewhere.^{5,7,18,24} Next, participants were asked whether there were "any other reasons why you avoid seeing your doctor," and either wrote their response in a small box if completing a mail survey or stated their response to an interviewer, who summarized their response, if completing a phone survey. Responses were brief and typically consisted of a short phrase or sentence. Interpretable responses were provided by

1,369 participants (58.8% of those who reported avoidance in response to the initial question). Eight participants provided uninterpretable responses either because they failed to provide a reason (e.g., "don't know") or because it was impossible to determine the motivation (e.g., "ambivalence" or "family tradition"), with 164 participants listing more than one reason.

Data Management and Analytic Approach

An independent research company was contracted to preliminarily clean the participant-generated responses ($n=1,377$; see 7 for a report of these uncoded responses) by using short phrases to standardize responses (e.g., "Busy" and "I'm too busy to go to the doctor" were recoded into "Too busy"). A prior study reported the top five of these uncoded responses (i.e., preference for self-care or alternative care, dislike or distrust doctors, fear or dislike of medical treatments, time, and money) and predictors of these responses.⁷ For the present study, the three study authors analyzed these short phrases provided by the research company in conjunction with participants' raw responses using a general inductive data analysis approach, a method in which a theory or conceptual model is developed through an iterative process of coding, grouping codes into categories based on underlying concepts, and forming a model or generating hypotheses based on the data.^{28,29} Coding was conducted by discussion of each participant response among all three authors; in rare cases when two authors disagreed, the third author acted as arbiter. Through this process, the authors identified emergent codes and collapsed and re-conceptualized existing codes as necessary. After assigning codes, all authors participated in an iterative process of placing codes into sub- and superordinate categories. The goal of the coding and categorization was to identify conceptually distinct factors underlying reasons for avoiding medical care, and to organize these factors into a conceptual framework that could provide targets for intervention and stimulate further research on avoidance. Upon completing the coding and categorizing, we reviewed existing theory on care-seeking and avoidance to determine whether our data provided support for a pre-existing theory or whether we should develop a new theory and/or model. We provide quantitative counts of the number of respondents, listing each reason in order to convey the frequency of responses, and qualitatively describe themes to provide context and explanation.

RESULTS

Among participants who indicated avoiding medical care, characteristics of those who provided qualitative responses ($n=1,369$) compared to those who did not ($n=958$) are shown in Table 1. Participants who provided responses were more likely to be white, female, younger, married, born in the U.S., to have completed the survey by phone, and to have higher income and education, but were less likely to have health insurance. Of the 1,369 participants who provided interpretable "other" responses, fewer than half (43.5%, $n=595$) endorsed at least one researcher-identified reason (answered

Table 1 Characteristics of Participants Who Reported Avoiding the Doctor and Either Did or Did Not Provide an Interpretable Qualitative “Other” Reason for Avoidance

	Provided qualitative “other” reason		χ^2 value, p value
	Yes ($n=1,369$)	No ($n=958$)	
	n (%)	n (%)	
Age	48.9 (14.9) *	52.7 (17.8)*	$t(2301)=5.63, p<0.001^\dagger$
Gender			$\chi^2(1)=5.49, p=0.02$
Male	547 (40.0)	429 (45.8)	
Female	822 (60.0)	528 (55.1)	
Marital status			$\chi^2(1)=4.95, p=0.03$
Married or living as married	781 (57.1)	496 (44.8)	
Not married	555 (40.5)	427 (44.6)	
Education			$\chi^2(3)=96.84, p<0.001$
Less than high school	115 (8.4)	165 (8.3)	
High school graduate	302 (22.1)	299 (31.2)	
Some college	442 (32.3)	254 (26.5)	
College graduate	478 (34.9)	204 (21.3)	
Household income			$\chi^2(5)=37.41, p<0.001$
\$0 to \$9,999	76 (5.6)	75 (7.8)	
\$10,000 to \$19,999	139 (10.2)	135 (14.1)	
\$20,000 to \$49,999	362 (26.4)	284 (29.7)	
\$50,000 to \$74,999	242 (17.7)	132 (13.8)	
\$75,000 to \$99,999	154 (11.3)	85 (8.9)	
\$100,000 or more	224 (16.4)	98 (10.2)	
Race/ethnicity			$\chi^2(6)=40.56, p<0.001$
Hispanic or Latino	116 (8.5)	115 (12.0)	
White	1028 (75.1)	597 (62.3)	
Black or African American	101 (7.4)	113 (11.8)	
American Indian or Alaska Native	12 (0.9)	12 (1.3)	
Asian	28 (2.0)	34 (3.6)	
Native Hawaiian or other Pacific Islander	3 (0.2)	5 (0.5)	
Biracial	27 (2.0)	26 (2.7)	
Nativity			$\chi^2(1)=8.53, p=0.003$
Born in the United States	1206 (88.1)	795 (83.0)	
Not born in the United States	131 (9.6)	127 (13.3)	
Health insurance status			$\chi^2(1)=15.72, p<0.001$
Yes	1073 (78.4)	805 (84.0)	
No	281 (20.5)	134 (14.0)	
Personal history of cancer			$\chi^2(1)=4.77, p=0.03$
Yes	114 (8.3)	104 (10.9)	
No	1227 (89.6)	820 (85.6)	
Survey response mode			$\chi^2(1)=38.92, p<0.001$
Mail	642 (46.9)	575 (60.0)	
Telephone	727 (53.1)	383 (40.0)	

Note: Percentages do not sum to 100 because of missing data

* Variable is continuous and values indicate mean (standard deviation)

† Test of comparison is t test

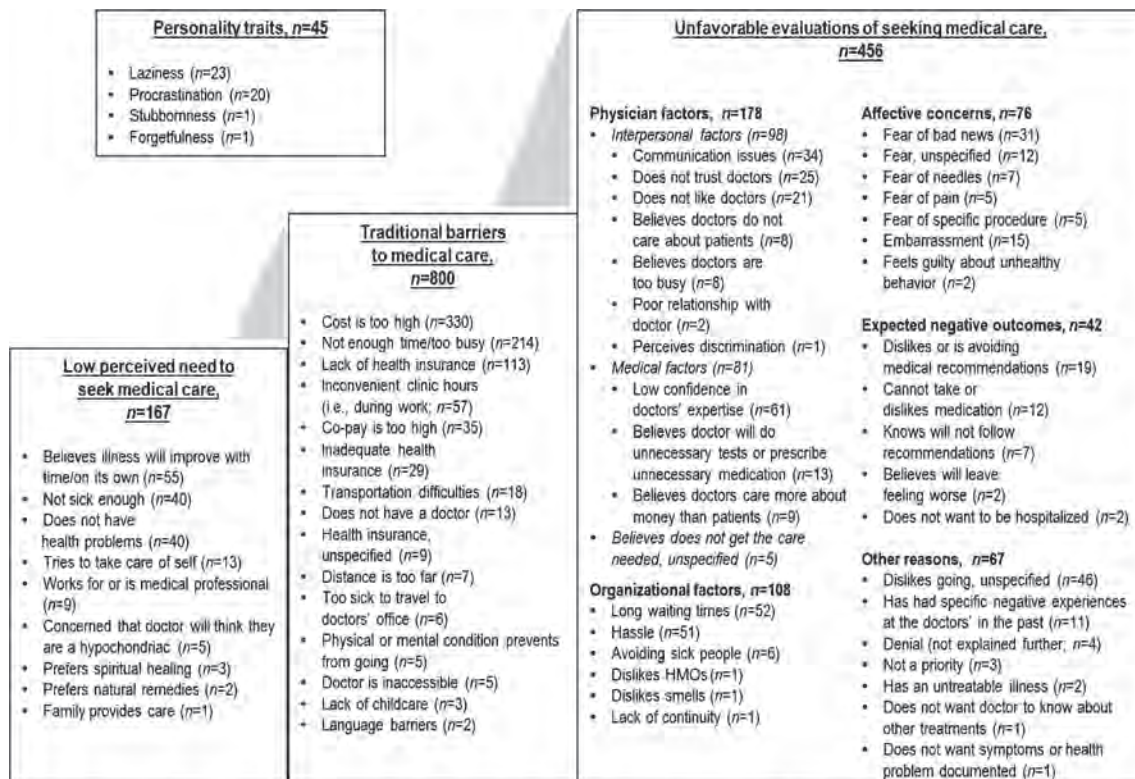
"agree/strongly agree" versus "disagree/strongly disagree") for avoiding medical care. Approximately one-fourth reported avoiding medical care because of feeling uncomfortable (26.8%, $n=369$) or fearing a serious illness (26.4%, $n=363$), with substantially fewer reporting avoiding medical care because it made them think of dying (8.2%, $n=113$).

From the analysis of participant-generated qualitative reasons for avoiding the doctor, we identified three overarching, conceptually distinct categories of reasons for avoiding medical care based on whether participants perceived seeking medical care to be necessary, available to them as a course of action, and favorable or beneficial. In the first category, "low perceived need to seek medical care," responses indicated a determination that seeking medical care was unnecessary. In the second category, "traditional barriers to medical care," responses indicated that seeking medical care was not an option because of a lack of resources. In the third category, "unfavorable evaluations of seeking medical care," people

evaluated some aspect of the care-seeking process as negative. A fourth category, labeled "personality traits," was also identified as a reason for avoidance that did not fall into any of the three major categories. Each category and relevant subcategories are described in detail below and outlined in Fig. 1.

Low Perceived Need to Seek Medical Care

Many responses, coded as "low perceived need," indicated the belief that seeking medical care was unnecessary ($n=167$). The most common reasons were that medical problems would either "improve over time" or "improve on their own" ($n=55$; e.g., "Whatever the symptoms, time will make it better"; "I believe the body will heal itself in most cases"). Participants often indicated that this was contingent on the problem not being very serious (e.g., "What I have will pass. I only go if I think it is serious"), with many stating not being "sick enough" as a reason for avoiding medical care ($n=40$;



Note: N's for overarching categories represent the number of unique respondents who gave a response in that category. Because some participants gave multiple reasons in one category, the number of responses given for specific reasons may total more than the overall number of responses for a particular category.

Figure 1 Participant-generated reasons for avoiding medical care (n=1,369).

e.g., “Don’t go unless there is a real need”). Despite the question stem referring to avoiding the doctor “when you think you should go,” many participants said they avoided medical care because they did not have health problems (n=40; e.g., “Not sick. If not broken don’t fix”). A small subset of participants also reported avoiding medical care because they “try to take care of themselves” (n=13; e.g., by using over-the-counter medication), were either a doctor or worked in a health care setting (n=9), were afraid to be labeled a hypochondriac (n=5), or preferred to rely on spiritual healing (n=3) or to use natural remedies (n=2).

Traditional Barriers to Medical Care

The largest overarching category of reasons for avoidance of medical care may be best described as “traditional barriers to medical care” (n=800, 58.4%). In this category, we included responses indicating circumstances or obstacles limiting access to medical care. Participants reported having too little time or being too busy to seek medical care (n=214), that clinic hours were inconvenient (n=57; e.g., “Have to take time off from work”), that transportation was difficult (n=18) or the distance was too far (n=7), that they were too sick to travel to the doctor’s office (n=6), or that an existing physical (n=5; e.g., multiple sclerosis) or mental health (e.g., depression, severe anxiety) problem prevented them from going. Financial reasons included concerns about overall cost (n=330), co-pays

(n=35), and health insurance (n=151). Few reported not having a doctor (n=13), that their doctor was inaccessible (n=5; e.g., “I don’t see him, I just see nurses, he is never there”), not having childcare (n=3), or language barriers (n=2).

Unfavorable Evaluations of Seeking Medical Care

Approximately one-third of participants (n=456, 33.3%) provided responses that demonstrated unfavorable evaluations of the process or outcomes of seeking medical care.

Physician Factors. The most frequently reported reasons for unfavorable evaluations were factors related to physicians (n=178). There were two major categories of physician factors: interpersonal concerns (n=98) and concerns about the quality of medical care (n=81). The most frequent interpersonal concerns involved communication concerns (n=34), including perceptions that doctors do not follow-up, that communication is difficult, disliking *how* doctors communicate (e.g., “Doctors often make you feel like you’re stupid”), disliking the *manner* in which doctors provide advice or recommendations (e.g., “Tired of being chewed out for not following medical advice”), perceiving that doctors do not listen to patients (e.g., “They are impersonal—paying more attention to computers”; “My experience is one of not being heard/considered”), and perceiving that doctors do not take patients’ concerns seriously. Other interpersonal reasons

included general mistrust of doctors (e.g., “I just don’t trust them”; $n=25$), believing that doctors do not care about patients (e.g., “I don’t always feel that they *truly* care”; $n=8$), and perceiving that doctors are too busy ($n=8$). Participants also reported a broad dislike of doctors, without elaboration ($n=21$).

The most frequent reason concerning the quality of medical care was that participants had low confidence in doctors’ expertise ($n=61$), which included beliefs that doctors would not be able to diagnose patients (e.g., “Fear that they won’t know what’s wrong either”), that doctors would provide incorrect diagnoses (e.g., “They usually make the wrong diagnosis”), and that doctors simply “make things worse.” This category also included more general statements about a lack of confidence in medical providers (e.g., “No confidence in today’s medical field”). Participants also expressed concerns that doctors would prescribe unnecessary tests or medication ($n=13$), and several participants stated that “doctors care more about money than patients” ($n=9$).

Organizational Factors. Many reasons for unfavorable evaluations concerned aspects of the medical system ($n=108$), such as long waiting times ($n=52$) and “hassle” ($n=51$), which included the hassle of making timely appointments (e.g., “Usually can’t see doctor at the time of a problem”) or even making appointments at all (e.g., “Difficult to get appointment, office too busy”), as well as general hassle (e.g., “It’s a big bother”). Several participants reported not wanting to be around sick people ($n=6$). Additional reasons are shown in Fig. 1.

Affective Concerns. Some participants reported that anticipated fear, embarrassment, or guilt kept them from seeking medical care ($n=76$). Responses concerning fear included the fear of receiving bad news ($n=31$) such as a medical diagnosis or a prognosis concerning an already diagnosed condition (e.g., “Afraid they might say my diabetes is worse”). Participants also reported fear of needles ($n=7$), pain ($n=5$), and specific procedures such as surgery or prostate exams ($n=5$), or simply reported “fear” ($n=12$). Relatedly, participants reported the specific emotion of embarrassment ($n=15$), including embarrassment about weight ($n=4$), health issues ($n=2$), or general feelings of discomfort ($n=9$). Finally, some participants reported feeling guilty about potentially disclosing engagement in unhealthy behavior ($n=2$).

Expected Negative Outcomes. Some responses pertained to beliefs that the outcome of seeking medical care would be negative, including dislike of a provider’s medical recommendations or the perception that recommendations would not be useful ($n=42$). These responses included avoidance of specific recommendations to change behavior ($n=19$); participants often disliked the emphasis on weight loss ($n=10$; e.g., “Hearing the same old—lose weight” and “Always have to hear about how fat I am”) or other health problems such as alcohol consumption, smoking, or high blood pressure. Some participants indicated they disliked or could not take medication ($n=12$; e.g., “I hate Rx drugs—the side effects scare me”) or that they would not follow a physician’s recommendations ($n=7$). Additional responses are reported in Fig. 1.

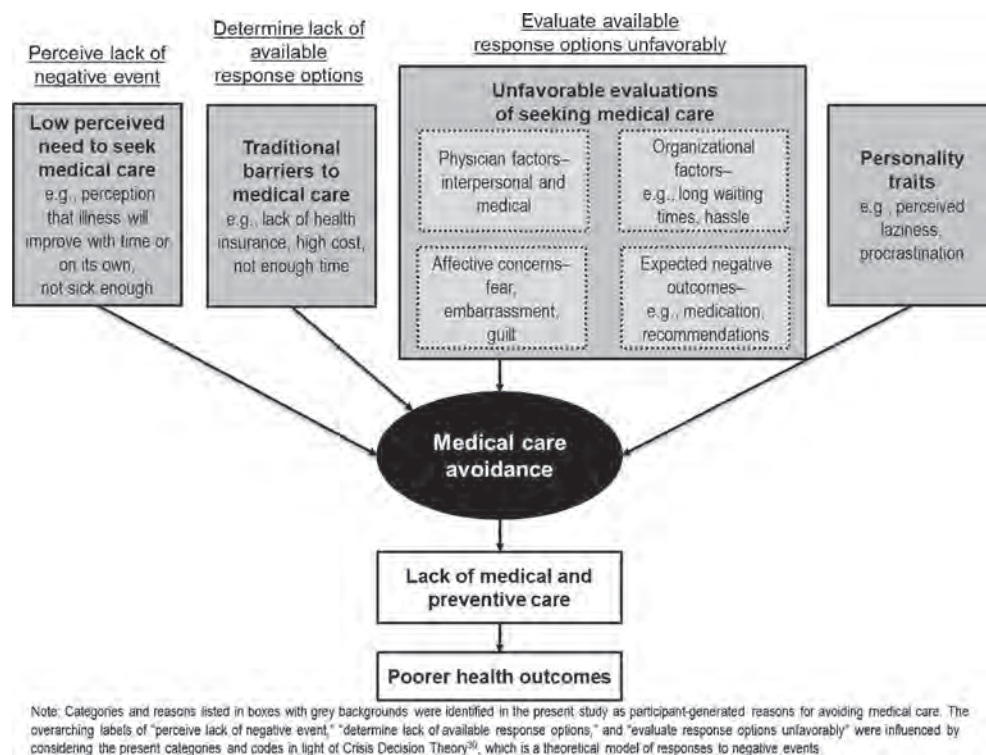


Figure 2 Conceptual model of medical care avoidance.

Other Reasons. Several additional reasons were reported that were either nonspecific or did not fall into another category ($n=67$). The majority of these responses included generally not liking or wanting to go to the doctor ($n=46$). Participants also reported having had past negative experiences but not specifying the nature of these experiences ($n=11$), denial ($n=4$), and not viewing seeking medical care as a priority ($n=3$). Fig. 1 presents other reasons reported by few participants.

Self-Ascribed Personality Traits

A fourth category of reasons for avoiding medical care concerned personality traits ($n=45$). Specifically, participants responded that they were “lazy” ($n=23$) or that they “procrastinate” ($n=20$), with little elaboration. Two additional responses are shown in Fig. 1.

Conceptual Model of Medical Care Avoidance

Fig. 2 presents the conceptual model of medical care avoidance that emerged from our categorization of participant-generated reasons. The language used to describe this model, as well as the conceptualization of avoidance at different stages of the care-seeking process, was influenced by Crisis Decision Theory, which describes how people respond to negative events more generally.³⁰ Our conceptual model proposes that avoidance may begin prior to noticing a need (e.g., avoidance of early detection or preventive services) or in the process of evaluating symptoms, or that avoidance can occur after a need is identified if people perceive a lack of resources, evaluate medical care unfavorably, or have a personality trait that discourages care-seeking. The model also proposes that avoiding medical care for any of these reasons would lead to a lack of medical and preventive care and, ultimately, poorer health outcomes. A specific comparison of our model of medical care avoidance to the more general Crisis Decision Theory³⁰ is presented in the Discussion.

DISCUSSION

This study presents the first comprehensive qualitative analysis of reasons for avoiding medical care among the general U.S. public. Using a diverse nationally representative sample and participant-generated responses, we applied inductive qualitative research methods to identify and categorize reasons for and to develop a conceptual model of medical care avoidance. Three overarching categories of reasons emerged based on the necessity, availability, and desirability of care-seeking: 1) low perceived need to seek medical care; 2) traditional barriers to medical care, in which people may want to seek care but are limited in their ability to do so; and 3) unfavorable evaluations of seeking medical care, in which people may perceive care-

seeking as necessary and an available option, but not desirable. Notably, unlike much of the prior research, the reasons identified here are applicable across a broad range of clinical settings and are particularly relevant for primary care. Primary care settings are patients' first point of contact for most health issues, and increasingly function as the hub of all medical care.³¹ Understanding why people fail to make it through the clinic door is critical to extending the reach and effectiveness of patient care.

Many of the reasons identified here are consistent with factors previously described in prior research, including studies of smaller patient and community samples, and reflected in theories of health behavior and health care use.^{1-4,7,10,11,32-37} Interestingly, the categories of reasons that emerged from the present study mapped almost directly onto a general psychological model of responses to negative events—Crisis Decision Theory³⁰—which has not previously been used as a framework for understanding medical care avoidance. Crisis Decision Theory posits that people respond to negative events first by appraising the severity of threat, next by identifying available response options, and lastly by evaluating available response options.³⁰ Putting our results into the language of this framework, participants who reported low perceived need to seek medical care may have appraised little threat or perceived high control to respond to the “crisis” themselves. Participants who reported factors limiting access may have felt that their response options were limited and that seeking medical care was not an option. Participants who reported unfavorable evaluations of medical care may have moved beyond both of these stages—they may have recognized a need to seek care (sufficient threat) and perceived seeking care to be a feasible option, but—in the language of Crisis Decision Theory—did not expect the gains of seeking care to outweigh the costs.

Our conceptual model proposes that perceptions of the necessity, availability, and desirability of seeking medical care may be prime intervention targets for reducing medical care avoidance. Although in some cases participants may have correctly assessed that their symptoms would go away with time or heal on their own, low perceived need to seek care suggests a need to educate patients on how to recognize symptoms for common health problems and the value of medical screening for asymptomatic conditions. For example, many people falsely believe they can tell when their blood pressure is high.³⁸ Education about the importance of seeking preventive health care and regular checkups is critical. Public health efforts might include telephone or printed client reminders that medical visits are vital to health maintenance, that regular checkups can identify risk factors and problems before they become serious, and that treatments are often more effective when disease is caught early.³⁹ Interventions utilizing technology such as telemedicine and eHealth (e.g., patient portals) may increase patient engagement with health care, provided they facilitate awareness of health care services and disease management.^{40,41} In terms of symptom appraisal, research should assess whether people must reach certain thresholds prior to seeking care.

Traditional barriers limiting access to or ease of seeking medical care, such as lack of health insurance and time

constraints, were the most commonly cited reasons for avoiding medical care, consistent with prior research.^{7,21,22,42–44} With the advent of the Affordable Care Act (ACA), lack of health insurance may become less of a barrier, but our results indicate that *inadequate* health insurance and high co-pays are also reasons for avoiding medical care, as well as numerous other reasons that may not be abated by the ACA. Interventions targeting these barriers are an important area for continued research. Strategies designed to tackle multiple barriers simultaneously (e.g., case management, financial incentives such as cost-reduction strategies or efforts to limit out-of-pocket costs) and comprehensive approaches addressing multiple patient needs (e.g., multidisciplinary team care⁴⁵) may be more effective in reducing avoidance than strategies that target only one barrier.

Finally, many people reported unfavorable evaluations of seeking medical care (e.g., communication problems, concerns about physicians' trustworthiness and expertise), consistent with prior research showing the impact of the patient-physician relationship and medical trust on medication adherence, health care utilization, and health outcomes.^{7,32,46–50} Much intervention research is focused on improving patient experiences and communication,^{51–55} and the frequency of responses indicating dislike of both physicians and the health care system confirms that this intervention focus is well-deserved. However, we also observed a variety of other reasons, such as avoiding specific recommendations or procedures, which could also be addressed through interventions aimed at changing negative perceptions about specific aspects of medical care.

Limitations and Future Directions

There are several important limitations of the present study. Medical care avoidance due to discomfort with physical examinations, fear of having a serious illness, and associating doctors with death may have been underestimated because these factors were assessed with closed-ended questions immediately prior to the open-ended question analyzed here. The pattern of differences in demographic factors among individuals who did and did not provide written reasons for avoiding seeking medical care suggest that responses were provided more often by people who may have been more favorably disposed to participate in research (e.g., those with higher incomes and education levels). Given the subjective nature of qualitative coding, alternate categorizations of the data are possible. In particular, reasons categorized here as "unfavorable evaluations of seeking medical care" have been conceptualized elsewhere as "cognitive barriers."¹⁵ Few participants self-identified as members of racial and ethnic minority groups or were born outside the U.S., which is important because the breadth and distribution of reasons for medical care avoidance may be different among these populations. For example, although language is a strong barrier for many immigrant populations,⁵⁶ only two participants identified language as a reason for avoiding care. Therefore, care should be taken to study reasons for avoidance among these specific populations.

Further, we cannot be certain that all respondents understood or paid attention to the exact item wording. We interpreted responses concerning "no health problems" as evidence for avoiding preventive screening or routine checkups. However, this is an extrapolation, and participants' intentions cannot be known.

In addition to informing intervention development, the present results are intended to generate hypotheses for future research. Participants tended to list only one response and were not encouraged to report all reasons that were important to them. If some people avoid medical care for multiple reasons, this may have reduced the overall reported prevalence of many reasons. Research is also necessary to test whether there is a linear decision-making strategy as suggested by Crisis Decision Theory, as it is possible that various reasons may interact and co-occur. For example, traditional barriers may exert more influence, or symptoms may be interpreted as less severe, when people negatively evaluate some aspect of care-seeking, (e.g., fearing bad news). Prospective research in which participants report symptoms and behavioral responses as they unfold would provide valuable insight into the process of decision-making surrounding avoidance. Researchers can also follow up on specific reasons that have been understudied and develop validated scales of reasons for medical care avoidance, and future research should test the predictive validity of these reasons for actual avoidance. Quantitative analyses are necessary because people cannot always accurately report their motivations⁵⁷ and might not be fully aware of the specific reasons they avoid seeking medical care. The frequency of specific reasons reported here might overestimate or underestimate the impact of these reasons on actual avoidance. Finally, asking people to explain why they choose to seek medical care in some instances but not in others might provide better understanding of the potentially nuanced and dynamic patterns and processes of decision-making.²

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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BAILES

EXHIBIT 21

Association of cancer worry and perceived risk with doctor avoidance: an analysis of information avoidance in a nationally representative US sample

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Abstract Fear of receiving bad news about one's health can lead people to avoid seeking out health information that, ironically, may be crucial for health maintenance. Using a nationally representative US sample, the present study examined whether perceived likelihood of developing cancer and worry about cancer were associated with reports of avoiding visits to one's doctor, in respondents under and over age 50. Cancer worry, but not perceived risk of cancer, predicted doctor avoidance in respondents aged 50 and older, whereas the opposite pattern held for respondents under age 50. Moreover, in respondents aged 50 and older, cancer worry and perceived cancer risk interacted such that cancer worry was linked to doctor avoidance only when respondents also perceived a high likelihood of cancer. The latter result is consistent with the notion that worry may motivate information *seeking* when people expect information to dispel worry and information *avoidance* when the information is seen as highly likely to confirm one's fears. Findings suggest a need for communication strategies that can influence worry and perceived risk differentially. Research should also assess the effectiveness of other behavioral strategies (e.g., automatic scheduling of appointments) as a means for reducing doctor avoidance.

Keywords Information avoidance · Doctor avoidance · Risk perception · Worry · Cancer

Introduction

People sometimes avoid seeking out information, particularly when they expect to have difficulty coping with the information and when the information may necessitate changes in behaviors or beliefs (Melnik & Shepperd, 2012; Howell & Shepperd, 2012; Sweeny et al., 2010). Karlsson et al. (2009) documented this “ostrich effect” in the financial domain, finding that investors less frequently checked their portfolios when markets were doing poorly. In medical contexts, this phenomenon manifests itself as people failing to make use of genetic tests and recommended screenings and delaying seeking medical care for symptoms and abnormalities that may portend significant health problems (Ropka et al., 2006; Keogh et al., 2004; Centers for Disease Control and Prevention, 1997). Such avoidance can be associated with negative outcomes such as disease progression and, in the case of communicable illnesses, disease spread (e.g., Vargas, 2001). It eventually leads to significant costs including increased morbidity and mortality, lost working days and reduced productivity, and increased healthcare expenditures (Byrne, 2008).¹

Despite interest in the robustness of information avoidance and its health implications, important questions remain about the causes and correlates of this phenomenon. For instance, in their recent review of the literature, Sweeny et al. (2010) noted that information avoidance is moderated by expectations about the content of information, with information avoidance being more likely to occur when people expect the information to reveal

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¹ Lund-Nielsen et al. (2011) recently documented the tragic human costs of healthcare avoidance—what they referred to as an “avalanche of ignoring”—on a personal level in women with malignant breast cancer wounds.

something negative (e.g., Karlsson et al., 2009). At the same time, however, Sweeny et al. also reviewed evidence suggesting that negative expectations can motivate information *seeking* rather than avoidance, noting that, for instance, worrying about the possibility of developing breast cancer is a consistent predictor of the decision to screen (Hay et al., 2006). Sweeny et al. (2010) concluded that, “Sometimes people avoid information they expect might be bad, but other times they seek it” (p. 347).

The finding that negative expectations can lead to either information avoidance *or* information seeking suggests the operation of moderating factors. In particular, one source of inconsistency may be the lack of differentiation between cognitive and affective components of expectations. Cognitive risk perceptions (i.e., believing oneself to be susceptible to a risk) and affective responses to risk (e.g., worrying about a risk) tend to be only moderately correlated (Lipkus et al., 2005; Bjovatin et al., 2008), and recent research suggests that these components of expectations often have differential effects and can even interact with one another to influence behavior. For example, among adult smokers who worried little about getting lung cancer, high perceived risk of lung cancer logically predicted greater intentions to quit smoking longitudinally (Klein et al., 2009). For those high in worry, on the other hand, high perceived risk was *negatively* associated with quit intentions, suggesting that high perceived risk was counterproductive in this group. Similar effects have also been observed in the domains of diet and exercise: High perceived risk of cancer was associated with lower vegetable consumption and exercise frequency for those high—but not low—in cancer worry (Ferrer et al., 2013).

Based on such findings, we hypothesized that a similar interaction may occur in the domain of information seeking. That is, worry may motivate people to seek information if they have low levels of perceived risk, as information seeking would appear to be a useful way to reduce or eliminate one’s feelings of worry under such circumstances (e.g., Hay et al., 2006). However, for people high in perceived risk, worry may be counterproductive, instead motivating people to avoid the information that they expect will only confirm their fears. The latter account resonates with the Cognitive Avoidance Theory of Worry, which posits that worry can be advantageous in motivating escape or avoidance of harmful situations (when possible) but can also lead to internal, cognitive avoidance responses when behavioral avoidance is not possible (Borkovec et al., 2004). Such an effect, if observed in the realm of information avoidance, may help explain the differential effects of negative expectations on information avoidance and would have implications for strategies designed to reduce this phenomenon in medical contexts.

Research aims

The present study explored the interaction between worry and risk perceptions in predicting whether or not people avoided visiting their doctors. Despite the recent proliferation of new media channels and information sources, doctors remain the most trusted sources of health information in the United States (Hesse et al., 2010), and most people expect to receive information from doctors on a range of issues such as diagnosis, treatment, and general lifestyle factors (e.g., exercise and diet; Salmon & Quine, 1989; Hoffmann et al., 2013; Whitlock et al., 2002). Thus, the desire to avoid health information is thought to be a crucial motivator of healthcare avoidance, alongside other important factors such as cost (Byrne, 2008, p. 281; Howell & Shepperd, 2012, p. 141; Federman et al., 2005). Accordingly, doctor avoidance was taken as a proxy for information avoidance in the present study, with the important caveat that healthcare avoidance can also arise from other factors such as cost, a history of negative patient-provider interactions, embarrassment, language barriers, or local shortages of primary care (see Byrne, 2008, for an extensive review of predisposing factors; Moore et al., 2004; Phillips et al., 1998).

As predictors, the present study examined worry and risk perceptions concerning cancer, one of the most feared diseases in the United States (American Association for Cancer Research, 2000). As mentioned, although risk perceptions and worry both refer to expectations about risk, risk perceptions conventionally involve a cognitive or deliberative assessment of a potential threat whereas worry entails an affective response to perceived vulnerability (Hay et al., 2006; McCaul et al., 1996). Given that worry about cancer has been cited variously as a facilitator and an inhibitor of cancer screening behavior (Consedine et al., 2004), we tested whether people who worry about cancer were more or less likely to report avoiding visiting their doctor. Similarly, risk perceptions have been found to have mixed effects on behavior, leading to health protective behaviors in some contexts but not others (Brewer et al., 2007; Gerrard et al., 1996). Thus, we also examined the link between perceived cancer risk and doctor avoidance. Moreover, we also tested whether cancer risk perceptions and cancer worry interacted to predict doctor avoidance, hypothesizing that cancer worry would predict more avoidance when people had a high perceived likelihood of cancer.

Furthermore, the present study examined whether the links between doctor avoidance and cancer worry and risk perceptions varied by age. Specifically, primary analyses were conducted among people aged 50 and older, as cancer rates are known to increase with age, with age 50 representing a critical point for increasing incidence and

mortality rates (Howlander et al., 2012; Cancer Research UK, 2012). Moreover, cancer-related education, vigilance, and medical screening and intervention efforts often focus on the over-50 population (e.g., NIA, 2010; USPSTF, 2008, 2009). For such reasons, some previous analyses of cancer worry and risk perceptions in national samples have been restricted to respondents aged 50 and over (e.g., McQueen et al., 2008). Importantly, however, concerns about cancer are not unique to people over age 50, and cancer worry and perceived risk of some types of cancer may actually *decrease* with age (e.g., age under 50 predicted increased worry in women at risk for breast cancer; Loescher, 2003; Orom et al., 2010; Katapodi et al., 2004). Also, recent studies have suggested the need to assess whether models of risk perception and worry generalize across different age groups (Consedine et al., 2004; Klein et al., 2009). Accordingly, secondary analyses were conducted among respondents under age 50 to test whether the results from the main analyses held in people with a lower need for cancer vigilance.

Finally, the present study tested whether any observed effects of cancer worry and risk perceptions on doctor avoidance were attenuated when analyses controlled for beliefs about whether detecting cancer early increases curability. The purpose of this analysis was to examine whether the observed effects of worry and risk perceptions were due to confounds with perceptions of cancer curability. For instance, people who believe detecting cancer early has no mortality benefit (i.e., low perceived curability) may tend to worry more about cancer and may also avoid situations such as doctor visits and screenings that could lead to a cancer diagnosis (Melnik & Shepperd, 2012; Dawson et al., 2006).

Methods

Data source and participants

Data were obtained from the National Cancer Institute's 2008 Health Information National Trends Survey (HINTS), a national health communication survey designed to monitor trends in the use of health information and communication technologies, as well as access to and use of cancer-related information. The survey collects data from a nationally representative sample of the US civilian, non-institutionalized adult population over the age of 18. Details of survey development, design, and methodology have been published elsewhere (Cantor et al., 2009; Nelson et al., 2004; Rutten et al., 2007). The survey instrument is available at: <http://hints.cancer.gov/instrument.aspx>.

Data were collected from January 7, 2008, through April 27, 2008. In an effort to address declining response rates for random digit dialing (RDD) telephone surveys (Cantor et al., 2009), HINTS 2008 used a dual-frame sampling design: One frame used RDD techniques to identify households for computer-assisted telephone interviews, and one frame used the US Postal Service listing of residential addresses to identify a stratified cluster sample of households to receive a mail survey. The overall response rates for the RDD and address frames were 24.2 and 31.0 %, respectively. In both survey frames, sample weighting procedures were used to account for respondents' probability of being selected, to adjust for nonresponse bias, to reduce the sampling variance of estimators, and to produce statistically valid standard errors for estimators (see below; Cantor et al., 2009, pp. 7.1–7.10).

Measures

Doctor avoidance was measured using the item: "Some people avoid visiting their doctor even when they suspect they should. Would you say this is true for you, or not true for you?" Response options were "True" or "Not true." Cancer risk perceptions were reported on a 5-point scale: "How likely do you think it is that you will develop cancer in the future?" Consistent with previous analyses (Ferrer et al., 2013), this item was re-coded into a 3-point scale from "1 = low" (combining "very low" and "somewhat low") through "2 = moderate" to "3 = high" (combining "somewhat high" and "very high").² Cancer worry was assessed using the measure: "How often do you worry about getting cancer?" To reduce skew, responses were reduced to a dichotomous variable, with people who reported worrying "rarely or never" coded as 0, and people who reported worrying "sometimes," "often," or "all the time" coded as 1 (Ferrer et al., 2013; Waters et al., 2010).³ Perceived curability of cancer when detected early was assessed based on respondents' agreement with the statement: "Cancer is an illness that when detected early can typically be cured" (4-point scale from 1 = "strongly

² Analyses conducted without recoding cancer risk perceptions led to results consistent with what is reported here.

³ Only 7.9 and 2.6 % of respondents reported worrying about cancer "often" or "all the time," respectively. Recoding the worry item reduced skew (adjusted Fisher-Pearson standardized moment coefficient) from 1.08 to -0.03. Using an alternative transformation method such as log transformation to reduce skew has been argued to be inappropriate for Likert-type data, because the scale is interval rather than ratio and values between scale points tend to be unequal (see, e.g., Nevill & Lane, 2007). Moreover, the dichotomous coding of worry in the present study allows for a comparison between those who report worrying *any* with those who do not, which has been found to be a meaningful categorization (Ferrer et al., 2013; Waters et al., 2010).

disagree” to 4 = “*strongly agree*”). Standard measures were used to elicit sociodemographic information, including gender, age, annual household income, highest level of education attained, and race or ethnicity. Health insurance status was assessed by asking respondents whether they “have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicare.”

Analysis

Given that HINTS 2008 used dual modes of administration (RDD and address frames), analyses were first conducted to test for potential differences in reports of doctor avoidance across sampling frames. To account for the complex sampling design, a separate set of 50 jackknife replicate weights was applied to each survey frame. Given no significant difference in reported doctor avoidance by frame, we aggregated the sample and employed a single, combined set of 50 jackknife replicate weights for the analyses reported here, as recommended (Moser et al., 2009; Rizzo et al., 2008). Analyses were conducted using SUDAAN version 10.0.1 (RTI International, Research Triangle Park, NC).

Hierarchical weighted binary logistic regressions were first used to examine the associations of cancer worry and cancer risk perceptions with doctor avoidance in respondents aged 50 and older. To do so, a main effects only model was estimated first, which included cancer worry, cancer risk perceptions, and sociodemographic characteristics, including gender, age, education, annual household income, race or ethnicity, and health insurance status. Ratings of cancer curability were then added to the model to test whether perceived curability explained any observed effects of cancer worry and cancer risk perceptions. Next, to test whether the effect of cancer worry depended on respondents’ level of perceived risk, we estimated a separate weighted binary logistic regression that contained all demographic variables, the main effects of cancer worry and cancer risk perceptions, and the interaction between cancer worry and cancer risk perceptions. Ratings of cancer curability were then added to the model to test whether the interaction term remained significant.

Subsequently, a parallel set of analyses was conducted in respondents under age 50 to explore whether the results extended to this age group. Lastly, an analysis was conducted among the entire sample to test whether age group (under vs. over age 50) significantly moderated the interaction between cancer worry and cancer risk perceptions. This was accomplished by regressing reports of doctor avoidance on all sociodemographic variables, cancer worry, cancer risk perceptions, a dummy variable for age group (0 = under age 50; 1 = aged 50 or over), all two-

way interactions between the age stratification dummy variable, cancer worry, and cancer risk perceptions, and the three-way interaction between the age stratification dummy variable, cancer worry, and cancer risk perceptions.

Results

Respondents aged 50 and older

Table 1 shows the demographic characteristics of the sample stratified by age group. Doctor avoidance was reported in a significant portion of respondents aged 50 and older, with 29.4 % indicating that they avoided visiting their doctor even when they suspected they should. As shown in Table 1, significant predictors of doctor avoidance among those aged 50 and older included low income, low education, younger age, and not having health insurance. Cancer worry, but not perceived cancer risk, was associated with reports of doctor avoidance. When perceptions of cancer as curable when detected early were added to the model, perceptions of curability were negatively associated with doctor avoidance ($OR = 0.77$, $p = .001$). However, adding perceptions of cancer curability to the model did not attenuate the effect of cancer worry on doctor avoidance ($OR = 1.35$, $p = .005$).

As predicted, in respondents aged 50 or over, cancer worry and cancer risk perceptions interacted to predict doctor avoidance (see Table 1). Figure 1 displays the nature of the interaction. As observed in other domains, cancer worry was particularly problematic when it was paired with high cancer risk perceptions. A simple slopes analysis (Aiken & West, 1991) revealed that the slope of the relationship between cancer worry and doctor avoidance differed significantly from zero when cancer risk perceptions were one standard deviation above ($B = 0.48$, $t(3,435) = 3.92$, $p < .001$) but not below ($B = 0.02$, $t(3,435) = 0.14$, $p = .888$) the mean.⁴ Similarly, separate weighted logistic regressions found that, for people with low or moderate cancer risk perceptions, cancer worry was unrelated to doctor avoidance ($OR = 1.10$, $p = .630$, and $OR = 1.39$, $p = .109$, respectively). For those with high cancer risk perceptions, however, cancer worry was positively related to doctor avoidance ($OR = 2.33$, $p = .014$). The interaction between cancer worry and cancer risk perceptions remained ($OR = 1.42$, $p = .040$) even after controlling for perceived curability of cancer ($OR = 0.74$, $p < .001$).

⁴ Simple slopes were calculated using unweighted data, which was necessary in order to generate the covariance matrix for coefficients.

Table 1 Effects of demographic characteristics, cancer worry, and perceived cancer risk on self-reported doctor avoidance, stratified by age group

Characteristic	Age 50 and over			Age under 50		
	<i>n</i> (%)	<i>OR</i>	<i>p</i> value	<i>n</i> (%)	<i>OR</i>	<i>p</i> value
Gender						
Male	1,837 (45.9)	1.09	.350	1,108 (50.5)	1.41	.019
Female	2,813 (54.2)	1.00	–	1,836 (49.5)	1.00	–
Education						
Some high school or less	468 (16.8)	1.00	–	207 (11.9)	1.00	–
High school graduate	1,464 (34.1)	0.88	.458	729 (32.0)	1.35	.169
Some college	1,040 (24.4)	0.63	.012	737 (31.3)	0.97	.880
College graduate	1,480 (24.7)	0.51	.001	1,140 (24.8)	1.06	.813
Annual household income						
< \$20,000	718 (20.2)	1.00	–	410 (19.4)	1.00	–
\$20,000 to <\$35,000	704 (19.1)	0.85	.285	351 (15.2)	1.03	.914
\$35,000 to <\$50,000	533 (14.0)	0.71	.085	337 (14.0)	1.05	.810
\$50,000 to <\$75,000	711 (19.0)	0.81	.243	489 (19.2)	0.76	.231
\$75,000 or more	1,049 (27.8)	0.68	.034	988 (32.1)	0.71	.148
Race/ethnicity						
Non-Hispanic white	3,538 (78.2)	1.00	–	1,878 (63.7)	1.00	–
Black/African American	380 (10.6)	0.88	.528	297 (11.8)	0.75	.217
Hispanic	245 (6.8)	0.67	.060	374 (16.8)	1.18	.292
Other	201 (4.3)	1.02	.929	219 (7.7)	0.96	.857
Age (years)						
18–34				1,113 (51.0)	1.00	–
35–49				1,831 (49.0)	1.06	.679
50–64	2,451 (58.4)	1.00	–			
65–74	1,189 (21.2)	0.63	.001			
> 74	1,010 (20.4)	0.41	<.001			
Has health insurance						
Yes	4,221 (91.2)	1.00	–	2,379 (77.2)	1.00	–
No	341 (8.8)	1.64	.005	527 (22.9)	1.61	.013
Cancer worry						
Yes	2,165 (50.6)	1.41	.003	1,514 (51.6)	1.20	.136
No	2,271 (49.4)	1.00	–	1,309 (48.4)	1.00	–
Perceived cancer risk		1.05	.510		1.25	.007
Low	1,774 (41.6)			1,059 (38.9)		
Moderate	1,723 (41.7)			1,125 (41.9)		
High	751 (16.8)			585 (19.3)		
Cancer worry × perceived cancer risk		1.42	.042		0.75	.101

Values represent unweighted counts (*n*) and weighted percentages (%). *OR*s and *p* values are from weighted logistic regressions predicting self-reported doctor avoidance. For those aged 50 or over, adding the interaction between cancer worry and perceived cancer risk caused Cox & Snell R^2 to increase from .051 to .054 and increased the model's goodness-of-fit ($\chi^2 = 9.3$, $df = 1$, $p < .01$); for those under age 50, Cox & Snell R^2 increased from .045 to .047, as did goodness-of-fit ($\chi^2 = 5.48$, $df = 1$, $p < .02$)

Respondents under age 50

Doctor avoidance was highly prevalent among respondents under age 50, with 40.4 % reporting that they avoided visiting their doctor even when they suspected they should.

As shown in Table 1, significant predictors of doctor avoidance in this age group included male gender and not having health insurance. Unlike in respondents over age 50, perceived risk of cancer, but not cancer worry, was associated with doctor avoidance. Perceptions of cancer as

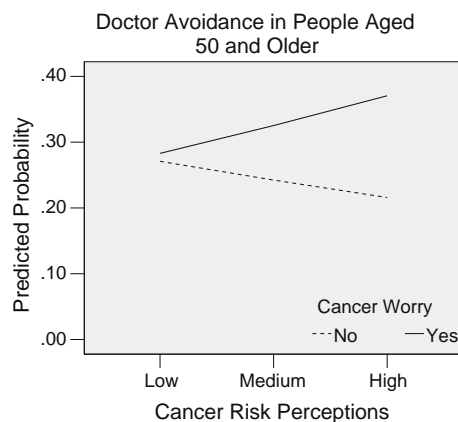


Fig. 1 Among respondents aged 50 and older, the relationship between cancer worry and doctor avoidance was stronger for people whose cancer risk perceptions were high

curable when detected early were marginally associated with doctor avoidance among those under age 50 ($OR = 0.86$, $p = .078$). Adding perceptions of cancer curability to the model did not attenuate the effect of cancer risk perceptions on doctor avoidance ($OR = 1.24$, $p = .012$). When the interaction between cancer worry and perceived cancer risk was added to the model, the interaction term did not approach significance (see Table 1).

Age group as moderator

In a logistic regression including all demographic characteristics, a dummy variable indicating whether respondents were under or over age 50 (0 vs. 1, respectively), the main effects of cancer worry and cancer risk perceptions, all two-way interactions between the age group dummy, cancer worry, and cancer risk perceptions, and the three-way interaction between age group, cancer worry, and cancer risk perceptions, the latter three-way interaction emerged as significant ($OR = 1.83$, $p = .014$). Adding the three-way interaction term to a model containing all main effects and two-way interactions significantly increased the model's goodness-of-fit ($\chi^2 = 12.40$, $df = 1$, $p < .001$). This suggests that the two-way interaction between risk perceptions and worry indeed varied significantly across the two age groups.

Discussion

A large segment of the US population may be vulnerable to late detection of illnesses due to psychological variables surrounding the receipt of negative health information. In the present study, 29.4 % of respondents aged 50 or over and 40.4 % of respondents under age 50 reported avoiding visiting their doctor even when they suspected they should.

In those over 50, such reports were related to cancer worry, with people who worried about getting cancer being more likely to report avoiding their doctor. On the other hand, in those under age 50, reports of doctor avoidance were positively related to cancer risk perceptions rather than worry. These findings suggest that doctor avoidance is indeed associated with affect and cognitions concerning cancer, but that such variables may operate differentially for younger adults compared to the middle-aged and older adults who are often the focus of cancer-related education and vigilance efforts (e.g., NIA, 2010; McQueen et al., 2008).

Importantly, in respondents aged 50 and older, the effect of cancer worry on doctor avoidance was qualified by an interaction with cancer risk perceptions, such that cancer worry alone did not appear to motivate doctor avoidance. Rather, worry was associated with doctor avoidance only when it was paired with high perceived likelihood of cancer. This adds potential nuance to the literature on information avoidance, which has documented cases in which negative expectations about the content of information motivate information *seeking* as well as cases in which negative expectations motivate information *avoidance* (e.g., Consedine et al., 2004; Sweeny et al., 2010). The interaction between worry and perceived risk is consistent with the notion that worry may motivate health protective behaviors like information seeking when such strategies are expected to reduce worry (e.g., when an individual thinks he or she will not receive a cancer diagnosis) but may lead to information avoidance when people believe, on a cognitive level, that their fears are likely to be realized.

Furthermore, the moderating effect of age on the cancer worry by perceived cancer risk interaction also suggests an additional factor that may moderate the impact of health expectations on information avoidance. In the present analyses, age was hypothesized to be relevant because of the increasing objective risk of cancer and growing need for vigilance and screening as people age (e.g., Howlader et al., 2012; NIA, 2010). For younger respondents, even those who see themselves as at high risk for cancer (or who worry about one day getting cancer) may be unlikely to connect these cognitions and affect to their typical healthcare usage. Also, the present results suggest that other, more general factors may differentiate younger and older respondents. For instance, even among respondents over age 50, reports of doctor avoidance were much less common among older compared to younger respondents. There are a variety of potential explanations for this finding, such as that, because of the onset of chronic conditions, people may find it increasingly difficult to avoid doctors as they age, they may tend to overcome their fears or discomforts associated with healthcare, or they may

increasingly realize the value of prompt medical care. Follow-up studies are needed to replicate this result and to examine health information avoidance processes in samples spanning a wide age range.

Lastly, perceived incurability of cancer when detected early was also related to doctor avoidance in respondents aged 50 and older, whereas this link was only marginally significant in respondents under age 50. The former effect is consistent with the finding that people are more likely to avoid information when they believe it will be difficult to cope with the information (Melnik & Shepperd, 2012; Howell & Shepperd, 2012). For example, Dawson et al. (2006) found that people were likely to seek diagnostic testing for diseases that were described as serious and treatable but were likely to avoid testing for diseases that were described as serious but untreatable. Importantly, however, the effects of cancer worry, cancer risk perceptions, and the worry-perceived risk interaction did not appear to be the product of confoundings between cancer incurability and cancer worry and risk perceptions, as the effects were not attenuated when analyses controlled for perceived incurability of cancer. That is, cancer expectations and perceived incurability of cancer appear to be independently related to doctor avoidance.

Implications for communicating about risk

The present study supports evidence in other domains indicating that worry and high perceived risk can be a volatile mix (Ferrer et al., 2013; Klein et al., 2009), and suggests that, in some contexts, it may be this unique combination of “negative expectations” that leads to the avoidance of information (whereas worry or high perceived risk alone may tend to motivate people to seek out information). This result has a potentially useful implication for communication about cancer and other health risks. In the over 50 population, intervention efforts aimed at increasing people’s cancer worry (e.g., as suggested in Hay et al., 2006) should take into account not only the audience’s existing propensity toward cancer worry, but also their existing level of perceived risk and the likely effect of the intervention on the level of perceived risk. For individuals low in perceived risk, worry may indeed function as a “cue to action” that encourages vigilance (Hay et al., 2006, p. 406). For those high in perceived risk, on the other hand, adding worry may cause people to delay seeking tests and advice for conditions that may be a harbinger of cancer. In such situations, it may in fact be beneficial to reduce or dampen risk perceptions rather than calling people’s attention to risk.

With growing interest in information sharing between patients and doctors, as well as increased use of decision aids prior to and during clinical encounters, it may be possible for doctors and clinicians to identify patients high

in cancer worry and to attenuate unrealistically high risk perceptions through personalized counseling (e.g., Braithwaite et al., 2004). Indeed, many communication skills training programs for physicians emphasize the benefits of inquiring about patients’ concerns prior to providing objective risk and disease information (Razavi et al., 2003). Importantly, however, communication and interventions aimed at reducing perceived risk may also alleviate worry, suggesting the need for continued research to develop and test communication strategies that can influence perceived risk without impacting worry, and vice versa (Portnoy et al., 2013).

Insights about the interactive effects of worry and perceived risk might also provide clues about why fear appeals—that is, attempts to scare people into adopting healthy behaviors—sometimes lead people to adopt health protective behaviors and sometimes lead to defensive avoidance. For instance, as Woloshin et al. (2012, p. 1677) noted, large-scale educational campaigns for cancer screening have tended to rely on a “simple recipe for persuasion” that involves provoking feelings of fear and vulnerability in the audience, with one recent ad in the *New York Times Magazine* proclaiming: “The early warning signs of colon cancer: You feel great. You have a healthy appetite. You’re only 50.” Importantly, such campaigns may not only produce worry but may also mislead people about their personal risk of cancer. As Woloshin et al. (2012, p. 1677) put it, “Many 50-year-olds who find this message scary may be surprised (and relieved) to learn that most 50-year-olds who feel great and have a healthy appetite do not have—and will not soon develop—colon cancer.” The results of the present study, although cross-sectional, suggest the possibility that campaigns that simultaneously provoke worry and inflate people’s perceived likelihood of cancer may lead to avoidant behavior in some members of the target audience, whereas campaigns that provoke worry without inflating people’s perceived likelihood of cancer (e.g., by acknowledging the low probability of cancer but emphasizing the potential costs of a missed detection) may be more effective in promoting screening and minimizing avoidance. Such an account may provide nuance to existing theories concerning fear appeals (e.g., the Extended Parallel Process Model; Witte, 1992), which consider the effects of emotional and cognitive evaluations of threat but do not systematically consider interactions between affect and cognition.

Default testing and screening

Doctor avoidance may be part of the reason why some people fail to receive recommended cancer screenings. Surveillance conducted by the Centers for Disease Control and Prevention suggests that, in some states, as few as

54.1 % of adults aged 50–75 years report being up-to-date with recommended colorectal test screening (CDC, 2010). One straightforward way to enhance uptake of beneficial medical tests may be to schedule tests automatically (with the option to cancel), thus making adherence to recommended testing the “default option” (Loewenstein et al., 2007). The results of the present study bolster this suggestion. Because cancer risk perceptions and cancer worry may be related to risk factors in a similar way (e.g., awareness of a relative’s colorectal cancer may simultaneously increase cancer risk perceptions and cancer worry; Glanz et al., 1999), some of the people who are the most likely to benefit from an early detection (i.e., based on their risk factors) may also be the most prone to avoiding their doctors. Given the wide range of important decisions for which default effects have been observed (e.g., Chapman et al., 2010; Johnson & Goldstein, 2003; Thaler & Sunstein, 2008), research is needed to determine whether requiring patients to cancel a pre-scheduled appointment (as opposed to simply neglecting to schedule one) may be an effective method for combating doctor avoidance, even when risk perceptions and worry are high.

Limitations

The present results are subject to several important limitations. First, although doctor avoidance was assumed to arise, in part, from people’s desire to avoid health information, there are also other reasons why people may avoid visiting doctors. For example, healthcare avoidance can arise from socio-ecological and contextual factors such as a lack of health insurance, shortages of primary care facilities in one’s area of residence, and experiences of discrimination in medical care (Federman et al., 2005; Phillips et al., 1998; Byrne, 2008; Casagrande et al., 2007). Although analyses in the present study controlled for the effects of income, health insurance status, race or ethnicity, and other sociodemographic characteristics, other known risk factors for doctor avoidance remained unaccounted for, such as rural geography (Vanderpool & Huang, 2010) and quality of the patient-provider relationship (Moore et al., 2004). Controlling for such factors may have helped adjust for non-information-related influences on reported doctor avoidance, thereby rendering it a better measure of health information avoidance.

Second, the present study’s use of cross-sectional data and correlational analyses precludes the determination of causality. It is possible that, for example, the link between cancer worry and doctor avoidance in people over 50 occurred because people who avoided their doctors missed opportunities to have their cancer worries assuaged. Indeed, in women at risk for breast cancer, genetic counseling has been found to assuage anxiety (Meiser &

Halliday, 2002), and women who avoid receiving information about their personal risk (Melnik & Shepperd, 2012) presumably miss out on such counseling. Alternatively, a third variable such as personality characteristics or a history of negative patient-provider interactions (Moore et al., 2004) may give rise to both cancer worry and doctor avoidance. For example, people high in the personality trait neuroticism are more likely than others to engage in avoidance coping in response to stressors (Bosworth et al., 2001), and they also tend to be higher in worry and anxiety concerning their health (Sörensen et al., 2008). Such an alternative explanation for the present findings would suggest different methods for reducing doctor avoidance, such as the need to train new coping skills or to reduce the stressfulness of medical encounters, rather than the need to manage patients’ cognitions and affect surrounding cancer risk. In order to establish a causal link between cancer expectations and doctor avoidance, further research is needed in which cancer risk perceptions and cancer worry are experimentally manipulated independently in order to observe their respective influences on doctor avoidance.

Third, the present study relied on self-reports of doctor avoidance, which may not reflect actual behavior. This is important given that people who avoid their doctor may devise excuses that conceal their true motives. For instance, “a woman who claims that she cannot find the time to get a suspicious mole looked at may in fact be avoiding a potentially scary diagnosis” (Sweeny et al., 2010, p. 347). If such duplicity rises to the level of self-deception, people may not recognize their own avoidance tactics and may therefore be unable to accurately report on them (see also Nisbett & Wilson, 1977, on “Telling more than we can know.”). To get around such issues, future research might replicate the effects observed in the present study using other measures such as cancer screening rates. Of course, such measures also present their own serious challenges and limitations. For example, a study examining cancer screening would have to be prospective and would need to control for previous cancer screening results, given that one might expect a link between previous screening and present cancer worry simply because of the information value of screening.

Finally, the present study was limited by single-item measures of worry and risk perception that did not tap all dimensions of these constructs. For instance, worry was assessed using a measure of frequency as opposed to intensity or amount. Although other studies have combined measures of worry frequency and amount into a single composite scale with high reliability (e.g., McCaul et al., 1996) and another study has found a similar interaction between worry and risk perception using a measure of worry amount as opposed to frequency (Klein et al., 2009), the present results require replication using other measures

of key psychological constructs. Such replication would present the opportunity to explore further nuances to the effects observed in the present study. It may be, for instance, that the actual experience of cancer worry is different across age groups or when risk perceptions are high rather than low, perhaps involving more rumination, depression, or anxiety (see Fresco et al., 2002, for an account of the relationships among these concepts).

Conclusions

Fear of receiving bad news about one's health can lead people to make decisions that, ironically, place their health at greater risk. Despite recent advances in the study of information avoidance (Howell & Shepperd, 2012; Melnyk & Shepperd, 2012), the factors that lead to this "ostrich effect" are still not well understood. However, the present study suggests that cancer worry and risk perceptions may underlie at least some types of information avoidance, and that, in people over 50, the detrimental effect of worry may arise primarily when people also perceive a high degree of risk. Interventions aimed at educating the public about possible carcinogens, the value of cancer screening in early detection, and other cancer related information may do well to avoid simultaneously increasing people's cancer risk perceptions and worry. When possible, communicators should also attempt to understand whether a particular audience is likely to be high in cancer worry, as such situations may call for efforts to moderate or dampen perceptions of the absolute risks involved or to explicitly address or attenuate affective responses to risk.

Conflict of interest None.

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BAILES

EXHIBIT 22

Predictors of Avoiding Medical Care and Reasons for Avoidance Behavior

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Background: Delayed medical care has negative health and economic consequences; interventions have focused on appraising symptoms, with limited success in reducing delay.

Objective: To identify predictors of care avoidance and reasons for avoiding care.

Methods: Using the Health Information National Trends Survey (2007), we conducted logistic regressions to identify predictors of avoiding medical visits deemed necessary by the respondents; and, we then conducted similar analyses on reasons given for avoidance behavior. Independent variables included geographic, demographic, socioeconomic, personal health, health behavior, health care system, and cognitive characteristics.

Results: Approximately one third of adults avoided doctor visits they had deemed necessary. Although unadjusted associations existed, avoiding needed care was not independently associated with geographic, demographic, and socioeconomic characteristics. Avoidance behavior is characterized by low health self-efficacy, less experience with both quality care and getting help with uncertainty about health, having your feelings attended to by your provider, no usual source of care, negative affect, smoking daily, and fatalistic attitude toward cancer. Reasons elicited for avoidance include preference for self-care or alternative care, dislike or distrust of doctors, fear or dislike of medical treatments, time, and money; respondents also endorsed discomfort with body examinations, fear of having a serious illness, and thoughts of dying. Distinct predictors distinguish each of these reasons.

Conclusions: Interventions to reduce patient delay could be improved by addressing the health-related behavioral, belief, experiential, and emotional traits associated with delay. Attention should also be directed toward the interpersonal communications between patients and providers.

Key Words: patient delay, delay stages, reasons for delay, care avoidance

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The proportion of Americans forgoing or delaying needed medical care rose considerably from 2003 (14%) to 2007 (20%),¹ despite the Healthy People 2020's "Access to Health Services" objective to reduce the proportion of Americans delaying necessary medical care.² Delay worsens prognosis, treatment options, and response to treatment for mental health,³ heart attack and stroke,⁴ many cancers,^{5–7} arthritis,⁸ urinary incontinence,⁹ and infectious diseases,^{10,11} among other conditions. When care is finally administered, more radical treatments are required, operation times and hospital length of stay increases, institutionalization becomes necessary, and a resource strapped system is further stressed, thereby, increasing health care costs.^{12–14} Although delays arise from processes occurring within the health care system, a considerable contribution to overall delay is made by the patient.^{4,11,15–19}

Interventions combating patient delay predominantly focus on improving knowledge of symptoms and understanding the need for medical care to treat the disease.²⁰ Although symptom and medical need awareness does increase, very few interventions actually produce a reduction in patient delay,^{4,21–26} presumably because medical care-seeking behavior is propelled by evaluative processes that convert symptom and need recognition to action.²⁷ Identification of symptoms and assessing medical need relate to only a portion of total patient delay—the appraisal and illness stages of delay as described by Safer et al.²⁷ The appraisal stage starts when one becomes aware of sensations and continues while the individual determines that the sensations are a sign of illness. The illness stage starts from recognition of illness to deciding whether medical care is required or would alleviate the symptoms. To inform future campaigns, all stages of the delay process should be understood; thus, in this study, we focus on the third and final stage, the utilization stage. The utilization stage occurs after determining that medical care is required, during which the individual decides whether the costs associated with medical care are manageable; these costs can represent any type of burden (eg, money, time, emotional, social). Few interventions have addressed the utilization stage.

The goal of this study is to examine characteristics associated with the utilization stage of patient delay (ie, delay subsequent to the individual's determination that experienced symptoms constitute a need for medical attention). After the appraisal and illness stages, an individual may avoid seeking care for a variety of reasons. They may be afraid of a potential diagnosis or treatment²⁸ or they may shirk pursuing care in the face of barriers in accessing the

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health care system.²⁹ Understanding this portion of patient delay will be useful in designing future interventions that incorporate strategies to overcome avoidance behavior once an individual recognizes the need for medical care. This stage is also germane to *all* diseases. Regardless of disease, individual sufferers may worry about the financial burden of medical care, the emotional costs of seeking care (eg, embarrassment, fear), or the time constraints on themselves or their family. In contrast, the appraisal and illness stages are linked to features of specific diseases such as symptoms and whether those symptoms indicate the need for medical care. Whereas currently interventions are conducted by disease affiliated researchers, future interventions could benefit from the combined efforts of various disease-specific programs to generate a collective message targeted at the utilization stage. In addition to identifying predictors of utilization stage care avoidance, in this study, we also identify specific reasons given for avoiding health care and the individual characteristics associated with these reasons.

METHODS

We used data from the 2007 Health Information National Trends Survey (HINTS) which is a nationally representative, cross-sectional survey of the noninstitutionalized adult population. This data contains 7674 observations (3582 by mail mode and 4092 by random-digit dial mode) of one randomly selected adult from each household in the sample. We also matched the Dartmouth Atlas' Hospital Referral Regions with HINTS' Designated Market Area variable to obtain the number of all types of physicians per 100,000 residents in the respondent's area.

Dependent Variables

The survey item: "Some people avoid visiting their doctor even when they suspect they should go. Would you say this is true for you, or not true for you?" was used to create a dichotomous outcome variable for patient delay. This item is positioned on the utilization stage of delay by asking about avoidance behavior once the respondent has determined they should get medical attention. That one is ill is determined at the end of the appraisal stage. That one requires medical care is determined at the end of the illness stage. It is only in the utilization stage, after determining that care is needed, that one can then avoid seeking care; it is impossible to avoid medical care when there is no need for it. All respondents who indicated they had avoided care were also asked about 3 specific reasons for their avoidance behavior: "I avoid seeing my doctor because I feel uncomfortable when my body is being examined," "I avoid seeing my doctor because I fear I may have a serious illness," and "I avoid seeing my doctor because it makes me think about dying." Three indicator variables were generated for respondents who "strongly agree" or "somewhat agree" with these 3 statements. In addition, after those 3 questions, respondents were asked, "Are there any other reasons why you avoid seeing your doctor?" There were 1377 responses to this question. We grouped the most prevalent types of responses: (1) preference for self-care or alternative care (eg, "believe in spiritual healing," "body will heal itself," "can

take care of myself," and "prefer alternative therapy"); (2) dislike or distrust doctors (eg, "feel intimidated," and "doctor's make things worse" in addition to "don't like doctors" and "don't trust doctors"); (3) fear or dislike of medical treatments (eg, "don't like taking medicine," "afraid of needles," and "don't want to be cut on"); (4) time; and (5) money. These outcome variables were coded as 1 if the reason was listed by the respondent and 0 otherwise.

Independent Variables

Our independent variables reflect characteristics that predispose or enable an individual to seek care.³⁰ These variables could also be used for reaching appropriate audiences, framing intervention messages, and addressing issues within the health care system itself (especially, the provider encounter). In addition to demographic and socioeconomic characteristics, we examine personal health, health behavior, health system, geographic, health belief, and cognitive variables. These health-related characteristics were often missing from formative research underlying previous interventions.^{4,23} Although traditional demographic variables provide information about which individuals to reach out to, the health-related variables such as behaviors, beliefs, and experiences are necessary to develop strategies that will effectively influence behavior.

Geographic independent variables include living in a metropolitan, urban, or rural county (Population Density) and the number of physicians per 100,000 residents (Physician Density). Demographic variables include sex, age, and race. Socioeconomic variables include education, income, insurance, employment, marital (includes living as married), and immigrant status.

Personal health variables include an indicator for reporting excellent or very good health (Health Status) as opposed to good, fair, or poor health; an indicator that the respondent feels overweight (Overweight); and an indicator for feeling sad, nervous, restless, hopeless, fatigued, or worthless all or most of the time (Negative Affect). Health behavior variables include an indicator for not exercising in the past month (No Exercise) and one for smoking daily (Smokes Daily).

Indicator variables depicting respondents' interaction with providers in the health care system during the past year include: respondent was always or usually able to ask questions (Questions), attention was always or usually paid to respondent's feelings (Feelings), providers always or usually involved respondent in health care decisions (Decisions), respondent always or usually understood the next steps to take care of their health (Next Steps), providers always or usually helped respondent with uncertainty about their health or health care (Uncertainty), and respondent felt they could always or usually rely on providers (Rely). Also an indicator was created for respondent rated the quality of health care they received as excellent or very good (Quality). Indicators for having a usual source of care (Usual Source of Care), and for using any complementary, alternative, or unconventional therapies during the past year (CAM) were included in the health care system category.

Cognitive variables include an indicator that the respondent is completely confident or very confident in their ability to take good care of their health (Health Self-Efficacy); an indicator for being completely confident or very confident in the ability to get health information (Information Self-Efficacy). We have health belief items related to 2 specific illnesses, obesity and cancer; these items are meant to convey general attitudes towards categories of disease. Cancer-related items are intended to demonstrate respondent's attitudes toward serious and potentially fatal diseases requiring intensive and invasive treatments. Obesity-related items, in contrast, tap into attitudes regarding a lifestyle health condition that is typically preventable and reversible. Similarly, beliefs related to the contribution of lifestyle behaviors to illness connect to respondents' sense of control over health and disease progression; in contrast, a sense of lacking control is measured by items that capture a belief in genetic predisposition toward disease and resignation or fatalism about disease. Health belief variables include the belief that: obesity is genetically inherited (Obesity Genetic); lifestyle or health behavior contributes to obesity (Obesity Behavior), exercise decreases the risk of cancer (Cancer and Exercise), cancer is most often caused by a person's behavior or lifestyle (Cancer and Behavior), and it seems like everything causes cancer (Cancer Resignation). A variable indicating that when the respondent thinks of cancer they automatically think of death (Cancer Fatalism), included among the health belief variables.

Statistical Analyses

The odds of avoiding the doctor were assessed using logistic regression. The primary goal of this study is to identify characteristics with any relation to utilization stage delay; this is accomplished with bivariate regressions, which present the total contribution of each characteristic to care avoidance. We also conduct multivariable logistic regressions to identify associations that persist when controlling for all other variables. Analyses of predictors for each of the 8 reasons respondents avoid a doctor visit were performed in the same manner. All analyses were conducted using Stata version 12.0. The HINTS uses a multistage sample design, thus we incorporate the jackknife replicate weights to adjust for the complex sample design.

RESULTS

Characteristics of the HINTS sample are presented in Table 1 along with summary statistics for those who delay necessary medical care and those who did not. Overall, 31% of adults in the HINTS sample (36% of the weighted sample) avoided doctor visits they had deemed necessary. Avoidance behavior was due to: preference for self-care or alternative care (3%), dislike or distrust of doctors (8%), fear or dislike of medical treatments (3%), time (16%), money (19%), discomfort with a body examination (33%), fear of a serious illness (34%), and thoughts of dying (13%). These 8 reasons capture 81% of avoiders.

Avoidance of a Doctor Visit Deemed Necessary

The predictors of avoidance are shown in Table 2 as unadjusted odds ratios as well as the odds ratios from the multivariable model. The majority of the geographic, demographic, and socioeconomic characteristics were associated with avoiding care in the unadjusted regressions. Living in an area with more physicians per capita reduced the odds of avoiding care, as did living in a more populated area. Being male and being employed were associated with higher odds of avoidance; greater age, income, and education as well as being insured and married were associated with lower odds of avoidance. However, these geographic, demographic, and socioeconomic characteristics were not independently associated with care avoidance (ie, the unadjusted associations did not persist in the multivariable regression).

In bivariate models, having excellent or very good health and having a usual source of care were related to lower odds of avoiding care; whereas smoking daily and having negative emotions were related to greater odds of avoiding care. All positive provider experiences were associated with lower odds of avoidance. Greater self-efficacy in taking care one's own health was associated with much lower odds of avoiding care. Variables indicating a low sense of control over health and disease progression (belief that obesity is genetically inherited, seems like everything causes cancer, and thoughts of cancer automatically lead to thoughts of death) were associated with greater avoidance. Whereas, a variable indicating greater sense of control (exercise decreases the risk of cancer) was associated with lower odds of avoidance.

Many of these associations persisted in the multivariable analysis suggesting independent contributions to avoidance. Specifically, respondents with higher health self-efficacy had 46% lower odds of avoiding doctor visits deemed necessary. Receiving high-quality care was associated with 30% lower odds of avoidance. Experiences with providers independently associated with avoidance behavior were: having your feelings attended to and getting help with uncertainty about health or health care. Help with uncertainty was associated with 30% lower odds of avoiding care. Although, when unadjusted, attendance to feelings from the provider was associated with lower odds of avoiding care, independently, it was associated with 51% greater odds of avoidance. Having an usual source of care was associated with 38% lower odds of avoidance, whereas negative affect, smoking daily, and fatalistic attitude toward cancer were associated with 46%, 31%, and 31% greater odds of avoidance, respectively.

Reasons for Avoidance of a Doctor Visit Deemed Necessary

Table 3 lists only the significant predictors of each reason for avoiding care. Again, the unadjusted odds ratios from bivariate models as well as the odds ratios from the multivariable model are presented. In this section, only the independent predictors from the multivariable analyses are discussed. There were demographic and socioeconomic characteristics independently associated with many of the reasons for care avoidance. Men who avoided care were less

TABLE 1. Summary Statistics for the HINTS Sample

	Full Sample	Avoiders	Nonavoiders
Mean and Percent (SD)	n = 7674	n = 2327	n = 5222
Geographic			
Physicians density (physicians per 1×10^5 capita range, 119.1–299)	205.21 (36.96)	204.48 (37.08)	205.57 (36.88)
Population density (%)			
Metropolitan	81	78	82
Urban	17	20	16
Rural	2	3	2
Demographic			
Male (%)	39	42	37
Age (range, 18–97)	54.16 (17.04)	50.45 (16.14)	55.74 (17.12)
Race (%)			
White	79	77	80
Black	10	10	10
Hispanic	6	7	5
Other	5	6	5
Married (incl: living as married)	59	57	61
Immigrant	11	11	10
Socioeconomic (%)			
Education			
Less than high school	9	12	8
High school graduate	55	57	53
College graduate	23	20	24
Postbachelor graduate	13	10	14
Income			
\$0–\$19,999	18	21	16
\$20,000–\$34,999	17	18	16
\$35,000–\$49,999	14	14	14
\$50,000–\$74,999	19	19	19
\$75,000–\$99,999	12	12	12
≥ \$100,000	20	16	22
Insured	88	82	91
Employed	51	57	49

HINTS indicates Health Information National Trends Survey.

likely than women to report having done so because of discomfort with the body examination or because of money. The insured had half the odds of citing “money” as their reason for avoiding care. However, the insured were at greater odds of avoiding care for certain nonfinancial reasons; namely, they had 3.71, 5.11, and 1.77 times the odds of reporting avoidance due to a preference for self-care or alternative care, dislike or distrust of doctors, and discomfort with body examinations, respectively. Respondents making between \$0–\$19,999 and \$20,000–\$34,999 annually had 4.85 and 5.22 times the odds of financially motivated avoidance, respectively, compared to those making over \$100,000 annually. However, lower income respondents were less likely to cite “time” as a reason for avoiding; those making between \$0 and \$19,999 annually had 76% lower odds of temporally motivated avoidance compared to those making over \$100,000 annually. Income is also significantly associated with reporting “fear of a serious illness” for avoiding care, with the middle income segment most likely to provide this reason. Less-educated respondents are more likely to avoid care because of thoughts of dying and because of fear of a serious illness, but less likely because of time.

Experiences with providers were also associated with specific reasons for avoiding care. Respondents who reported

that their provider paid attention to their feelings had one third the odds of stating a preference for self-care or alternative care as their reason for avoiding care and 2.23 times the odds of giving time as their reason. Respondents who reported that they could rely on their providers had 68% lower odds of avoiding doctors because they dislike or distrust them. Respondents who reported that their providers helped them understand the next steps in taking care of their health had 61% lower odds of avoiding doctors because of money. Other health-related characteristics associated with specific avoidance reasons were high health self-efficacy which conferred greater odds of citing the reason “preference for self or alternative care”; the belief that cancer is most often caused by a person’s behavior or lifestyle which was associated with greater odds of giving the reason “thoughts of dying”; and feeling overweight which had half the odds of citing money as the reason.

DISCUSSION

“Access to health care requires both that the population has access in terms of the availability of services and that people take the steps necessary to gain access. Individual behaviors thus form a key determinant of whether and when services are utilized but patient behaviors often do not

TABLE 2. Odds of Avoiding Doctor Visits Deemed Necessary

	Bivariate Regressions			Multivariable Regression		
	Odds Ratio	P	95% Confidence Interval	Odds Ratio	P	95% Confidence Interval
Geographic						
Physician density	0.997	0.022	[0.99–0.99]	0.999	0.372	[0.99–1.00]
Population density (reference: metropolitan)		0.013			0.150	
Urban	1.35		[1.08–1.68]	1.36		[0.97–1.90]
Rural	1.63		[1.02–2.61]	1.47		[0.77–2.80]
Demographics						
Male	1.31	<0.001	[1.13–1.52]	1.21	0.062	[0.98–1.48]
Age (reference: ≥ 65) (y)		<0.001			0.089	
18–39	2.36		[1.91–2.91]	1.49		[0.98–2.24]
40–54	2.22		[1.85–2.67]	1.53		[1.07–2.18]
55–64	1.68		[1.37–2.05]	1.16		[0.87–1.55]
Race (reference: white)		0.318			0.679	
Black	0.97		[0.74–1.27]	0.93		[0.60–1.44]
Hispanic	1.36		[0.97–1.88]	1.31		[0.76–2.26]
Other race	0.94		[0.64–1.35]	0.98		[0.53–1.78]
Married	0.81	0.012	[0.68–0.94]	0.99	0.906	[0.76–1.26]
Immigrant	1.01	0.937	[0.77–1.31]	0.79	0.414	[0.44–1.40]
Socioeconomic						
Education (reference: less than high school)		<0.001			0.932	
High school graduate	0.82		[0.64–1.05]	0.99		[0.65–1.50]
College graduate	0.67		[0.51–0.86]	0.99		[0.62–1.56]
Postbachelor graduate	0.52		[0.38–0.71]	0.89		[0.51–1.54]
Income (reference: ≥ \$1,00,000)		<0.001			0.826	
\$0–\$19,999	1.78		[1.37–2.29]	1.31		[0.81–2.09]
\$20,000–\$34,999	1.62		[1.23–2.12]	1.10		[0.73–1.65]
\$35,000–\$49,999	1.55		[1.19–2.00]	1.21		[0.78–1.86]
\$50,000–\$74,999	1.28		[0.99–1.65]	1.02		[0.69–1.49]
\$75,000–\$99,999	1.35		[1.06–1.70]	1.20		[0.86–1.66]
Insured	0.49	<0.001	[0.38–0.60]	0.68	0.075	[0.44–1.04]
Employed	1.26	0.007	[1.07–1.48]	1.28	0.080	[0.97–1.67]
Personal health						
Health status	0.66	<0.001	[0.56–0.77]	1.14	0.219	[0.92–1.40]
Overweight	1.08	0.275	[0.93–1.25]	1.10	0.411	[0.87–1.39]
Negative affect	1.95	<0.001	[1.61–2.34]	1.46	0.006	[1.11–1.89]
Health behaviors						
No exercise	1.15	0.082	[0.98–1.33]	0.97	0.784	[0.75–1.23]
Smokes daily	1.89	<0.001	[1.60–2.22]	1.31	0.030	[1.02–1.66]
Health care system						
Usual source of care	0.49	<0.001	[0.42–0.58]	0.62	<0.001	[0.48–0.80]
CAM	1.15	0.068	[0.99–1.33]	1.15	0.275	[0.88–1.49]
Experience with providers (in past 12 mo)						
Questions	0.45	<0.001	[0.35–0.58]	0.75	0.267	[0.44–1.25]
Feelings	0.62	<0.001	[0.51–0.74]	1.51	0.021	[1.06–2.12]
Decisions	0.49	<0.001	[0.38–0.62]	0.85	0.418	[0.57–1.25]
Next steps	0.57	<0.001	[0.45–0.70]	1.32	0.246	[0.82–2.11]
Uncertainty	0.52	<0.001	[0.43–0.62]	0.70	0.018	[0.51–0.93]
Rely	0.44	<0.001	[0.34–0.54]	1.11	0.625	[0.73–1.67]
Quality	0.42	<0.001	[0.35–0.48]	0.70	0.026	[0.50–0.95]
Health beliefs and cognitions						
Health self-efficacy	0.38	<0.001	[0.33–0.43]	0.54	<0.001	[0.42–0.69]
Information self-efficacy	0.63	<0.001	[0.54–0.73]	0.96	0.704	[0.79–1.16]
Obesity genetic	1.21	0.045	[1.00–1.45]	1.03	0.799	[0.80–1.33]
Obesity behavior	0.87	0.129	[0.73–1.03]	1.04	0.702	[0.83–1.31]
Cancer and behavior	1.04	0.607	[0.90–1.18]	0.93	0.469	[0.77–1.12]
Cancer and exercise	0.83	0.037	[0.69–0.98]	0.82	0.097	[0.64–1.03]
Cancer resignation	1.65	<0.001	[1.40–1.93]	1.18	0.131	[0.95–1.46]
Cancer fatalism	1.53	<0.001	[1.35–1.73]	1.31	0.001	[1.12–1.53]

CAM indicates complementary, alternative, or unconventional therapies.

conform to medical or managerial expectation of appropriate and timely service use.”³¹

Many of these individual behaviors occur during the utilization stage and are predicted by factors distinct from

those related to the appraisal and illness stages.²⁷ We examined predictors of utilization stage delay and the reasons for this delay using the HINTS survey in which respondents admitted to avoiding doctor visits when they thought they

TABLE 3. Statistically Significant Associations Between Reasons for Avoiding Doctor Visits Deemed Necessary and Respondent Characteristics

	Bivariate Regressions			Multivariable Regressions		
	Odds Ratio	P	95% Confidence Interval	Odds Ratio	P	95% Confidence Interval
Preference for self-care or alternative care						
Income (reference: $\geq \$100,000$)		0.024				
\$0–\$19,999	0.14		[0.03–0.66]			
\$20,000–\$34,999	0.10		[0.01–0.52]			
\$35,000–\$49,999	0.59		[0.20–1.68]			
\$50,000–\$74,999	0.57		[0.19–1.71]			
\$75,000–\$99,999	1.13		[0.33–3.78]			
Insured	6.79	0.006	[1.85–24.8]	3.71	0.001	[1.74–7.87]
Health status	2.33	0.019	[1.17–4.59]			
Negative affect	0.28	0.005	[0.12–0.65]			
No exercise	0.27	0.003	[0.11–0.60]			
Feelings				0.33	0.033	[0.11–0.91]
Rely	3.23	0.018	[1.26–8.20]			
Quality	2.75	0.015	[1.25–6.04]			
Health self-efficacy	2.73	0.021	[1.19–6.20]	2.88	0.036	[1.07–7.70]
Information self-efficacy	2.37	0.006	[1.31–4.25]			
Dislike or distrust of doctors						
Income (reference: $\geq \$100,000$)		0.008				
\$0–\$19,999	0.27		[0.14–0.52]			
\$20,000–\$34,999	0.58		[0.30–1.08]			
\$35,000–\$49,999	0.68		[0.15–3.11]			
\$50,000–\$74,999	0.80		[0.43–1.46]			
\$75,000–\$99,999	0.76		[0.37–1.53]	5.11	0.046	[1.03–25.3]
Insured	1.80	0.031	[1.07–3.02]			
CAM	0.34	<0.001	[0.20–0.58]			
Questions	0.37	<0.001	[0.20–0.65]			
Feelings	0.24	<0.001	[0.14–0.41]			
Decisions	0.25	<0.001	[0.12–0.48]			
Next steps	0.29	<0.001	[0.17–0.48]			
Uncertainty	0.22	<0.001	[0.11–0.41]	0.32	0.038	[0.10–0.93]
Rely	0.31	0.003	[0.14–0.64]			
Quality						
Thoughts of dying						
Race (reference: white)		<0.001				
Black	2.26		[1.40–3.65]			
Hispanic	2.36		[1.40–3.95]			
Other race	1.96		[0.74–5.17]			
Education (reference: less than high school)		<0.001				
High school graduate	0.42		[0.29–0.60]	0.30	0.032	[0.12–0.68]
College graduate	0.31		[0.18–0.50]	0.31		[0.10–0.86]
Postbachelor graduate	0.22		[0.12–0.39]	0.22		[0.07–0.64]
Income (reference: $\geq \$100,000$)		0.002				
\$0–\$19,999	3.23		[1.88–5.53]			
\$20,000–\$34,999	2.22		[1.23–3.99]			
\$35,000–\$49,999	1.48		[0.67–3.25]			
\$50,000–\$74,999	1.63		[0.83–3.15]			
\$75,000–\$99,999	0.90		[0.45–1.76]			
Health status	0.70	0.052	[0.49–0.99]			
Overweight	1.47	0.049	[1.01–2.14]			

(Continued)

TABLE 3. Statistically Significant Associations Between Reasons for Avoiding Doctor Visits Deemed Necessary and Respondent Characteristics (continued)

	Bivariate Regressions			Multivariable Regressions		
	Odds Ratio	P	95% Confidence Interval	Odds Ratio	P	95% Confidence Interval
Negative affect	2.40	<0.001	[1.63–3.53]			
No exercise	1.55	0.013	[1.11–2.17]			
Cancer and behavior	1.84	0.001	[1.29–2.62]	2.02	0.006	[1.23–3.31]
Cancer resignation	1.59	0.024	[1.07–2.34]			
Cancer fatalism	2.75	0.000	[1.76–4.29]			
Fear of a serious illness						
Race (reference: white)		0.001				
Black	1.87		[1.23–2.82]			
Hispanic	1.87		[1.16–2.98]			
Other race	1.59		[0.79–3.17]			
Education (reference: less than high school)		0.008			0.025	
High school graduate	0.63		[0.44–0.89]	0.47		[0.25–0.88]
College graduate	0.50		[0.34–0.73]	0.50		[0.22–1.11]
Postbachelor graduate	0.67		[0.40–1.11]	0.73		[0.29–1.79]
Income (reference: \geq \$100,000)		0.003			0.045	
\$0–\$19,999	1.49		[0.92–2.41]	0.97		[0.42–2.21]
\$20,000–\$34,999	1.46		[0.88–2.40]	1.22		[0.63–2.35]
\$35,000–\$49,999	1.90		[1.10–3.27]	1.82		[0.95–3.46]
\$50,000–\$74,999	1.28		[0.75–2.15]	1.38		[0.71–2.66]
\$75,000–\$99,999	0.67		[0.34–1.29]	0.68		[0.29–1.52]
Male	0.79		[0.63–0.98]			
Insured		0.039		1.88	0.040	[1.02–3.42]
Married (incl: living as married)	0.71	0.005	[0.55–0.89]			
Health status	0.63	0.003	[0.47–0.83]			
Overweight	1.59	0.002	[1.19–2.11]	1.87	0.003	[1.25–2.77]
Negative affect	1.88	0.000	[1.36–2.59]	1.75	0.046	[1.00–3.02]
No exercise	1.31	0.035	[1.02–1.68]			
Smokes daily	1.51	0.020	[1.07–2.11]			
Cancer fatalism	2.40	0.000	[1.81–3.17]	2.32	0.000	[1.52–3.54]
Discomfort with body examination						
Race (reference: white)		0.042				
Black	1.62		[1.05–2.50]			
Hispanic	1.23		[0.77–1.93]			
Other race	1.91		[1.06–3.40]			
Education (reference: less than high school)		0.024				
High school graduate	0.66		[0.47–0.93]			
College graduate	0.56		[0.36–0.84]			
Postbachelor graduate	0.53		[0.33–0.82]			
Income (reference: \geq \$100,000)		0.004				
\$0–\$19,999	1.70		[1.04–2.76]			
\$20,000–\$34,999	1.85		[1.09–3.14]			
\$35,000–\$49,999	1.55		[0.92–2.59]			
\$50,000–\$74,999	1.09		[0.63–1.88]			
\$75,000–\$99,999	0.85		[0.49–1.45]			
Male	0.50	<0.001	[0.39–0.63]	0.47	0.002	[0.29–0.75]
Insured				1.77	0.038	[1.03–3.02]
Employed	0.75	0.045	[0.56–0.98]			
Negative affect	1.40	0.032	[1.03–1.90]			

Cancer fatality	1.59	0.007	[1.15–2.19]			
Time						
Age (reference: ≥ 65) (y)		0.007				
18–39	1.48		[0.88–2.46]			
40–54	1.97		[1.31–2.94]			
55–64	1.34		[0.78–2.28]			
Race (reference: white)		0.024				
Black	0.63		[0.35–1.12]			
Hispanic	1.13		[0.55–2.28]			
Other race	0.57		[0.32–1.00]			
Education (reference: less than high school)		<0.001				
High school graduate	1.76		[0.89–3.45]			
College graduate	3.01		[1.47–6.12]			
Postbachelor graduate	5.81		[2.96–11.3]			
Income (reference: ≥ \$1,00,000)		<0.001				
\$0–\$19,999	0.12		[0.04–0.28]			
\$20,000–\$34,999	0.30		[0.13–0.65]			
\$35,000–\$49,999	0.24		[0.14–0.41]			
\$50,000–\$74,999	0.62		[0.39–0.97]			
\$75,000–\$99,999	0.71		[0.43–1.16]			
Physician density	1.01	0.015	[1.00–1.01]			
Insured	2.99	0.002	[1.56–5.71]			
Employed	2.36	<0.001	[1.61–3.46]			
Married (incl: living as married)	1.67	0.038	[1.04–2.67]			
Smokes daily	0.56	0.013	[0.35–0.86]			
Usual source of care	1.62	0.004	[1.18–2.22]			
Feelings						
Questions	1.72	0.008	[1.16–2.54]			
Information self-efficacy	1.46	0.029	[1.04–2.03]			
Money						
Physician density	0.996	0.035	[0.992–0.999]			
Population density (reference: metropolitan)		0.007				
Urban	2.06		[1.33–3.18]			
Rural	1.57		[0.67–3.69]			
Male						
Age (reference: ≥ 65) (y)		<0.001				
18–39	3.05		[1.81–5.13]			
40–54	3.91		[2.31–6.59]			
55–64	2.47		[1.43–4.25]			
Education (reference: less than high school)		0.003				
High school graduate	1.77		[1.04–2.99]			
College graduate	1.48		[0.81–2.68]			
Postbachelor graduate	0.77		[0.34–1.71]			
Income (reference: ≥ \$1,00,000)		0.003				
\$0–\$19,999	3.33		[1.75–6.30]			
\$20,000–\$34,999	3.51		[1.90–6.48]			
\$35,000–\$49,999	2.90		[1.56–5.36]			
\$50,000–\$74,999	2.94		[1.78–4.85]			
\$75,000–\$99,999	2.25		[1.13–4.48]			
Insured	0.41	<0.001	[0.30–0.54]			
Overweight						
Usual source of care	0.72	0.035	[0.53–0.96]			
Next steps						
Health self-efficacy	0.58	0.002	[0.42–0.80]			
Information self-efficacy	0.57	<0.001	[0.43–0.75]			
CAM indicates complementary, alternative, or unconventional therapies.						

should have gone. Focusing on each of the delay stages facilitates a more detailed view of the processes contributing to total delay and enables interventionists to design more effective programs.²⁷

An important finding from this study is that although demographic, socioeconomic, geographic, and psychographic characteristics are related to avoiding care during utilization stage delay, only psychographic characteristics persist in explaining avoidance when controlling for all traits. Interventionists should consider these more modifiable characteristics associated with delay such as health-related behaviors, beliefs, and experiences when designing programs.

Another relevant finding is that several very disparate reasons were provided for why respondents avoid necessary doctor visits. Money and time are the primary policy targets of delay related to access to care. For example, the Patient Protection and Affordable Care Act, addresses the issue of money by subsidizing coverage for low-income individuals³²; whereas states (eg, California) require organizations to offer appointments to patients in a timely manner³³ and other health care organizations have introduced “open” access scheduling; these systems have demonstrated significant reduction in waiting times.^{34–36} However, the most frequent responses for not seeking care were cognitive reasons: discomfort with a body examination and fear of a serious illness; and less frequently: thoughts of dying and fear or dislike of medical treatments. These reasons do not easily lend themselves to sweeping policy measures.

Other avenues may be exploited to address these reasons for care avoidance, such as: media campaigns, insurance carriers, and providers. Predictors of the reasons for care avoidance can be used to inform motivational messages appropriate for the audiences most likely to exhibit avoidance behavior. For example, messages that ameliorate fear of examinations, treatments, and diagnoses could attack many of the immobilizing cognitive pathways that lead to care avoidance. Regardless of reason, the strongest predictor of avoiding care is health self-efficacy. This is a characteristic that cannot be simply inserted into an informational package; however, experiments with manipulating self-efficacy have been found to increase the individual’s self-efficacy and improve achievement of a target behavior (eg, seeking care in a timely manner).³⁷ Images of others performing the target behavior, when included in a communication campaign can increase an audience member’s own sense of self-efficacy.³⁸

Self-efficacy is also closely related to the patient-activation concept³⁷ which encourages active, engaged patient-consumers and bucks the traditional “medical-model” which absolves individuals from investing in their health by becoming passive absorbers of provider expertise, compliant with provider judgment.^{39,40} Insurers and providers can work together and directly with patients to improve patient activation. Raising activation levels may be an important factor in improving access and reducing unmet medical need.^{41,42}

Insurers and providers could also work together to improve the patient encounter. Provider-patient interactions substantially affect patient satisfaction, compliance, and understanding.^{43–46} Three of the reasons for avoidance behavior (preference for self-care or alternative care, dislike or distrust

of doctors, and money) were predicted by less-than-ideal aspects of the provider-patient relationship (feelings not attended to, unable to rely on providers, and not understanding next steps). Insurers are a good resource for encouraging patient-centered communication as being insured is highly predictive of avoiding care due to preference for 3 reasons related to antipathy toward the medical encounter.

Limitations to this study include the age of the data; since 2007, when the data were collected, important changes have occurred in the US political and economic landscape. However, because many of the predictors of and reasons for avoidance are cognitive, external forces have little bearing on the mechanics of their influence. The survey only allowed a listing of reasons for avoiding care but not the level of importance respondents assign to these various reasons. This information would be useful in understanding which reasons are seen as the biggest obstacles and thus should be intervened on first. Finally, our measure of delay was self-reported and thus subject to recall bias.

In conclusion, a substantial portion of the population traverses the appraisal and illness stages of patient delay, concludes they require medical attention, only to become mired in the utilization stage. This study’s results alert interventionists that the independent associations with avoidance were of the health-related behavioral, experiential, and belief type. These modifiable characteristics provide actionable traits for health program developers to build interventions around. In addition, the study suggests that interventionists should broaden their attention to include interpersonal interactions between patients and providers.

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BAILES

EXHIBIT 23



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PSYCHOLOGICAL FACTORS RELATED TO DELAY IN CONSULTATION FOR CANCER SYMPTOMS

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SUMMARY

This research investigated psychological characteristics associated with delay in seeking help for symptoms of rectal cancer. Sixty nine subjects reconstructed pivotal events beginning with symptom onset and ending with medical consultation, and completed the Temperament and Character Inventory (TCI) and the State-Trait Anxiety Inventory (STAI). The mean delay time was around 6 months, with about 1 out of 6 subjects waiting one year or more. Subjects estimated the lengths of two sequential segments of total time to consultation: (1) Symptom Appraisal time (from symptom onset to recognition of possible seriousness), and (2) Action Appraisal time (from recognition of seriousness to medical consultation). Symptom Appraisal time accounted for over two-thirds of total time and was associated with low scores on the TCI Harm Avoidance scale (TCI-HA), indicating dispositional insensitivity to threat, and marginally associated with less education and younger age. Action Appraisal time was not associated with any demographic or psychological variables. Low TCI-HA scores were also associated with lower likelihood of previous cancer screening, and with better judgments of premorbid health. Low STAI Trait scores were associated with better judgments of premorbid health and fewer doctor visits. Results are discussed regarding the importance of understanding dispositional characteristics related to health behavior.

INTRODUCTION

Delay in seeking medical attention for symptoms signaling cancer has long been recognized as a conspicuous and serious problem. Broad causal attributions for delay can be made, with some of the cause attributable to the patient, some to administrative difficulties such as insurance or scheduling problems, and some to the physician(s) (Robinson *et al.*, 1984, 1986). Patient delay has often been related to 'contextual variables' (Facione, 1993), such as gender, marital status, and SES. The strongest evidence exists for longer patient delays to be associated with lower SES (Antonovsky and Hartman, 1974; Coates *et al.*, 1992; Hackett *et al.*, 1973; Ramirez *et al.*, 1999) and fewer years of education (Andersen *et al.*, 1995; Antonovsky and Hartman, 1974; Facione, 1993; Facione *et al.*, 2002; Ramirez *et al.*, 1999; Samet *et al.*, 1988). There is less consistent evidence for relationships between patient delay and gender (Antonovsky and Hartman, 1974; Langenbach *et al.*, 2003; Robinson *et al.*, 1986; Samet *et al.*, 1988), age (Andersen *et al.*, 1995; Antonovsky and Hartman, 1974; Arndt *et al.*, 2002; Cameron and Hinton, 1968; Facione, 1993; Langenbach *et al.*, 2003;

Meechan *et al.*, 2003; Nosarti *et al.*, 2000; Phelan *et al.*, 1992; Ramirez *et al.*, 1999; Samet *et al.*, 1988), and ethnic background (Coates *et al.*, 1992; Ramirez *et al.*, 1999).

In addition, it appears that many individuals delay for reasons that are more psychological in nature. There is recurring evidence for the existence of two principal, albeit contrary, reasons given by patients who were asked why they delayed in seeking help. The first is given by the person who believed that their symptoms *were not serious* and would clear up on their own, suggesting a rather complacent attitude toward their symptoms. The second is given by the person who was concerned that their symptoms *were serious*, but who was then immobilized by fear, embarrassment, or denial, suggesting that avoidance was the prime psychological deterrent (Andersen *et al.*, 1995; Byles *et al.*, 1992; de Nooijer *et al.*, 2001a, b; Hansen *et al.*, 1997; Moyer and Levine, 1998).

Refined studies of delay suggest that the former problem (i.e. thinking that the symptoms are *not serious*) is the greater impediment to help seeking. Such studies have demonstrated that segmenting the total time period into sequential ‘periods of delay’ can facilitate the search for specific causes (i.e. when the delay occurs and why) as well as differences between individuals regarding the principal cause of their delay (Andersen *et al.*, 1995; Antonovsky and Hartman, 1974; Safer *et al.*, 1979). These periods of delay are punctuated by critical psychological and behavioral junctures such as the recognition of seriousness of symptoms, the decision to seek medical attention, calling for an appointment, etc. This approach makes it possible to have patients estimate the time elapsed between these junctures so that, for example, it can be determined how long it took someone to call for an appointment once they had recognized the seriousness of their symptoms. In essence, this approach allows the differentiation of disparate causal factors that come into play as the person’s reactions, decisions, and behaviors unfold. Such research has shown that the segment of time that has been found to account for the longest portion of patient delay, 60–70% across all subjects, begins with the onset of symptoms and ends when the individual has determined that their symptom(s) may represent some significant medical condition (Andersen *et al.*, 1995; Cacioppo *et al.*, 1986; Jones, 1990). This period of time is that during which the individual is trying to determine the cause and significance of their symptom(s), and has thus been called ‘appraisal delay’. Because the symptom appraisal process accounts for the majority of total delay time, the psychological processes that occur during this time are of special interest (Andersen *et al.*, 1995). An individual might delay seeking treatment when their appraisal of their symptoms is influenced in part by an ‘optimistic bias,’ (Andersen *et al.*, 1995; Jones, 1990) ‘denial,’ (Moyer and Levine, 1998), or a health related ‘defensive bias’ leading to a psychological minimization of threat (Croyle *et al.*, 1997) and a more benign explanation of their symptoms.

The literature regarding individual differences in the perceptions of bodily changes has a long and robust history. In an early summary of their work on the incongruous relationship between objective and subjective health, Costa and McCrae (Costa and McCrae, 1985) concluded that the best explanatory model:

‘holds that the relation between complaints and medical conditions varies with the individual; that there are consistent and enduring individual differences in the perception, interpretation, and reporting of bodily symptoms; and that there is a continuum from persistent underreporting to frank hypochondriasis.’ (p. 20).

In addition, these authors and others have provided a substantial body of evidence to show that this ‘dimension of somatic concern’ (Costa and McCrae, 1985) correlates very strongly with a fundamental dimension of personality. The various researchers in this area, however, have provided slightly different perspectives on the psychological dimension of interest, variously referring to it as ‘Neuroticism’ (Costa and McCrae, 1992), ‘Negative Affectivity’

(Watson and Clark, 1984), or 'Trait Anxiety' (Cameron *et al.*, 1998). Granted these variations, however, there is general consensus on four interrelated themes: (1) there is a fundamental dispositional characteristic, or 'Negative Affective Trait' that is manifested in the degree of tendency toward anxiety, worry, and negative emotions in general (Cloninger, 1987; Costa and McCrae, 1992; Gray, 1994; Watson and Clark, 1984), (2) this trait correlates significantly with the frequency of somatic complaints, and the relationship between the two dimensions is fairly rectilinear from one extreme end to the other (Costa and McCrae, 1985), (3) somatic complaints are a function of both psychological disposition and medical conditions (Costa and McCrae, 1987; Leventhal *et al.*, 1996; Mechanic, 1979; Mechanic, 1980; Watson and Pennebaker, 1989, 1991), and (4) somatic complaints often correlate more strongly with dispositional factors than with objective medical assessments (Koller *et al.*, 1996; Watson and Pennebaker, 1989).

Most of the work on symptom appraisal has focused on the end of the continua where elevated levels of somatic complaints coincide with elevated levels of this negative affective trait, which is manifested in the problem of excessive and undue medical utilization (Kirmayer *et al.*, 1994). Conversely, however, a *dampened* response to bodily changes represents a very different sort of problem and illustrates the need to understand the other end of this dimension, where a person's somatic concern is insufficient at those times when it is medically warranted. One manifestation of a dampened response to bodily changes could be a delay in the recognition that one's symptoms could be serious, resulting in an overall delay in seeking medical consultation.

The present research

The present research was designed to investigate the role of negative affective traits in delayed help seeking for symptoms of rectal cancer. For the remainder of this paper we will adopt the term Trait Anxiety to describe the dispositional dimension of interest. While non-specific negative affectivity may be associated with frequency of somatic complaints, more specific attention to Trait Anxiety seems warranted (Watson and Clark, 1992). Antonovsky and Hartman, in their extensive review of delay in cancer, determined that both low and high levels of anxiety were associated with longer delay times (Antonovsky and Hartman, 1974). In addition, anxiety is the emotion that corresponds most directly to responsiveness to potentially threatening situations (Barlow, 1988; Beck *et al.*, 1985; Gray, 1994). A simplified model of delay time segmentation was distilled from the models described earlier in order to place emphasis specifically on the psychological aspects of patient delay. The point at which the individual recognizes that their symptoms could be serious is a critical psychological turning point in the time prior to seeking help. In the present model, then, there are three events of interest: (1) the point at which signs or symptoms were first noticed, (2) the point at which the patient decided that their bodily changes might be signaling some serious health problem, and (3) the point when the patient took concrete action by seeing their doctor or calling for an appointment. The first time period, called *Symptom Appraisal*, corresponds to Andersen *et al.*'s (Andersen *et al.*, 1995) 'appraisal delay.' The second time period, called *Action Appraisal*, corresponds to their 'illness delay' and 'behavioral delay' combined (see Figure 1).

A pilot study explored delay in the case of carcinoma of the rectum, which is a particularly troubling problem for two reasons. First, there are often salient and regularly occurring symptoms in rectal cancer, including a very high incidence of rectal bleeding as a first sign, which should provide a clear sign of trouble. And yet, many people who experience symptoms of rectal cancer wait inordinate periods of time before seeking help (Hansen *et al.*, 1997; Holliday and Hardcastle, 1979; Irvin and Greaney, 1977; MacArthur and Smith, 1984; Rubin *et al.*, 1980). Second, while the success rate for treatment of early-stage rectal cancer is very high, delay in seeking help for symptoms severely compromises that success

(Byers *et al.*, 1997; Winawer *et al.*, 1997). The pilot data ($n = 40$) indicated that the mean total time from symptom onset to medical consultation was 20.2 weeks (S.D. = 24.6; median = 9.0) and the mean Symptom Appraisal time was 14.9 weeks (S.D. = 21.3; median = 8.0), showing that Symptom Appraisal time accounted for 75.5% of the total time on average. Pilot analyses also revealed that those patients who took the longest time in Symptom Appraisal had very low scores on two measures related to Trait Anxiety. The patients who took one year or more in Symptom Appraisal all had scores below the 15th percentile on the Harm Avoidance scale of the Temperament and Character Inventory (TCI-HA) (Cloninger *et al.*, 1994) and scores below the 40th percentile on the Trait scale of the State-Trait Anxiety Inventory (STAI-T) (Spielberger *et al.*, 1970). The individual who took the longest to recognize the seriousness of their symptoms (2 years) had the lowest possible score on the STAI-T and was below the 10th percentile on the TCI-HA (see Materials section below for a description of these scales).

The following study was then undertaken with three purposes in mind. The primary purpose was to explicitly test the hypothesis that a low level of Trait Anxiety is associated with longer Symptom Appraisal times. The second purpose was to determine whether Trait Anxiety is associated with the length of time taken to actively get help once that realization had occurred (Action Appraisal). The third purpose was to explore associations between Trait Anxiety and indicators of broader patterns of health behavior.

METHOD

Participants and procedure

Participants were patients who had been diagnosed with primary rectal tumors and who had been treated in the Section of Colon and Rectal Surgery at the Washington University School of Medicine. Patients were recruited during a follow-up office visit soon after initial treatment, but were excluded if there was evidence of cognitive deficits that would have precluded reliable recall of the events of interest or that would have interfered with completion of the psychological instruments. Informed consent was obtained at that time.

Materials

A structured interview had been developed in the pilot work, but was subsequently converted to a self-report paper-and-pencil format that could be completed at home and returned by mail, which resulted in a marked increase in participation. The paper-and-pencil questionnaire was designed to collect information about history of symptoms, perceptions of those symptoms, pertinent decision-making and behaviors during the time period prior to medical consultation, as well as more general health behavior history. The questionnaire was made up of several sections of multiple-choice or checklist questions. The first section included questions about the nature of the initial symptoms and the patients' reactions to them. The next three sections included questions about the recognition of seriousness of symptoms, the decision to seek medical help, and the actual pursuit of medical help. These sections also included the questions that were used to estimate the lengths of the two time segments. Subjects were asked to think back on the time when they first thought or realized that their symptoms might be serious, and Symptom Appraisal time was estimated by asking, '*How long after your very first symptom did this occur?*' Action Appraisal time was estimated by asking, '*How long was it after your first symptom that you first saw or called a doctor about it?*' and then subtracting Symptom Appraisal time from this estimate. Both Symptom Appraisal and Action Appraisal times were measured as continuous variables (in weeks) so as to capture the most information (Facione, 1993).

Prior health care beliefs and practices were assessed in the next section with the following questions: ‘*Before these problems started, did you have a regular doctor?*’ ‘*How often did you go to your doctor before these problems began?*’ ‘*For what reasons did you see your doctor?*’ and ‘*How would you describe your overall health before you were diagnosed with cancer?*’ To assess prior cancer screening behavior, subjects were asked: ‘*Have you ever had screening for any kind of cancer?*’ and ‘*(If yes) What kind of screening have you had?*’ Finally, demographic information (age, education, ethnic background, gender) was documented, in order to test relationships between these variables and delay.

Trait Anxiety was assessed with two standardized psychological measures. The first was the short form (144 items) of the TCI (Cloninger *et al.*, 1994), which was developed out of Cloninger’s unified biosocial theory of personality (Cloninger, 1987). Based on theory as well as the pilot data discussed earlier, the Harm Avoidance scale (TCI-HA) was of particular interest. The TCI-HA scale measures individual differences in sensitivity to signals of possible threat, danger or punishment. Individuals who score high on the TCI-HA ‘are characterized as cautious, tense, apprehensive, fearful, inhibited, shy, easily fatigable, and apprehensive worriers,’ while individuals who score low on the TCI-HA ‘are confident, relaxed, optimistic, carefree, uninhibited, outgoing, and energetic’ (Cloninger, 1987, p. 576). In a study involving 5,903 Australian twins, the short TCI-HA scale demonstrated a Cronbach’s alpha ranging from 0.78 to 0.85 over four birth cohorts (Heath *et al.*, 1994). In the same study, test–retest correlations ranged from 0.73 to 0.84 over an average of 2.1 years. Cloninger’s model endeavors to tie measurable personality dimensions to heritable brain structures (Cloninger, 1987, 1998). In that regard, approximately 54% to 56% of the stable variation in TCI-HA scores has been shown to be determined by additive and nonadditive genetic influences in the same study of 2680 adult Australian twin pairs (Heath *et al.*, 1994). In addition, TCI-HA scores have been found to correlate in normal subjects with the surface area of the anterior cingulate gyrus (Pujol *et al.*, 2002) and with levels of serotonergic activity (Hansenne and Ansseau, 1999), both of which play a significant role in the processing of affective information (Rauch, 2003). The TCI-HA scale has been found to correlate very highly with measures designed by other authors to reflect the same broad theoretical construct (Cloninger *et al.*, 1994; Zelenski and Larsen, 1999), including the Neuroticism scales of the EPQ (Eysenck and Eysenck, 1976) and the NEO-PI (Costa and McCrae, 1992), the Punishment Expectancy scale of the GRAPES (Ball and Zuckerman, 1990), the BIS scale of the BIS/BAS (Carver and White, 1994), and the total score on the SCL-90 (Derogatis *et al.*, 1973).

The second instrument was the *State-Trait Anxiety Inventory* (Spielberger *et al.*, 1970), which is a well-known and widely used measure of symptoms of anxiety, both transitory and trait. Because we were interested in the role of stable dispositional characteristics, the Trait Anxiety scale (STAI-T) was of special interest. The STAI-T requires subjects to estimate how much of the time they typically experience various symptoms of anxiety. The STAI-T has also been found to correlate significantly with the TCI-HA scale (Cloninger *et al.*, 1994).

Statistical analyses

All analyses were done using SAS version 8.1. Means and frequency counts were used to describe initial responses to symptoms. Mean lengths of delay times were calculated, as were mean proportions of Symptom Appraisal times. Because of the pilot findings, the calculation of Action Appraisal time was based only on those subjects who suspected their symptoms were serious prior to seeking help.

Cox proportional hazards analysis was used to test whether Symptom Appraisal time was associated with the psychological scores, with the event of interest being the point at which

the subjects recognized the seriousness of their symptoms. Time-to-event analysis was used for two reasons (Kleinbaum, 1996). First, it is the method of choice with time-based measures, which tend to be non-normally distributed. Second, because it was expected that some subjects would not have suspected seriousness before getting help, as was found in pilot work, time-to-event analysis would allow inclusion of data points from subjects who did not reach the event of interest prior to medical consultation. These models also allow estimation of covariate effects. As mentioned previously, those pilot subjects who had scores in the lowest range on both the TCI-HA and STAI-T took the longest time in Symptom Appraisal. For that reason, scores on both measures were divided into tertiles—low, medium, and high.

Cox proportional hazards analyses were also applied to Action Appraisal time, but excluded any subjects who did not recognize the seriousness of their symptoms prior to seeking help. The purpose in isolating the Action Appraisal time was to uncover and study any evidence that *high* anxiety was associated with longer Action Appraisal times, which would suggest hesitation or avoidance in seeking help following suspicion of seriousness. Therefore, analyses regarding the Action Appraisal time period were done only on the subjects who recognized seriousness prior to medical consultation. Lastly, non-parametric Kruskal–Wallis analyses were used to look at the association between the two measures of Trait Anxiety and previous health related behaviors.

Results

Of the 100 subjects who were approached to participate in this study, 91 initially agreed to participate and 80 returned the questionnaire materials. Eleven of the 80 participants were asymptomatic prior to the discovery of the rectal tumor; the problem was first discovered during a routine medical examination or cancer-screening test. The remaining 69 subjects were symptomatic prior to seeking help, so data on these subjects are reported here.

Twenty-seven of the subjects were female and 42 were male. Sixty-five of the subjects were Caucasian and four were African-American. The age at diagnosis ranged from 33 to 85 years, with a mean of 61.3 (S.D. = 12.7) and a median age of 62. Level of education ranged from 1 to 20 years: 12 subjects did not complete high school, 26 completed high school, 18 completed at least some college or technical school, and 13 completed at least some graduate work.

Two-thirds of the subjects reported that their initial symptoms were either ‘barely’ (24/69; 34.8%) or ‘a little’ (22/69; 31.9%) noticeable, while the remaining subjects reported that they were ‘somewhat’ (13/69; 18.8%) or ‘very’ (10/69; 14.5%) noticeable. On the other hand, around 80% of the subjects initially believed that their symptoms were either ‘not’ (38/69; 55.1%) or ‘a little’ (17/69; 24.6%) serious, while the remaining subjects believed that they were ‘somewhat’ (10/69; 14.5%), ‘very’ (2/69; 2.9%), or ‘extremely’ (2/69; 2.9%) serious. Judgments of salience and seriousness were statistically related (Spearman’s rho = 0.24, $p = 0.0497$, two-tailed), but note that the judgments of seriousness were quite positively skewed, more than were the judgments of salience.

Regarding subjects’ initial attributions about the cause of their symptoms, the majority (49/69; 71.0%) did not believe that their symptoms were due to cancer, while only three subjects (3/69; 4.3%) believed that they were. The remaining subjects were either uncertain (16/69; 23.2%) or did not answer this question (1/69; 1.4%). Of those who thought their symptoms could be due to something other than cancer, most thought they had hemorrhoids (37/53; 69.8%). Others attributed their symptoms to diet (3/53; 5.7%), physical injury or

stress (5/53; 9.4%), or miscellaneous causes such as ulcers, diverticulitis, or other less-threatening medical conditions (8/53; 15.1%).

Six subjects indicated that they were unable to estimate the total time before consultation or the two time segments, leaving 63 subjects for these analyses. The total time from symptom onset to medical consultation ranged from less than a week to around 5 years. The mean total length of time was 25.0 weeks (± 40.4) and the median was 10.0 weeks. Eighteen of these subjects (28.6%) waited 6 months or more, while 11 of them (17.5%) waited one year or more from symptom onset to medical consultation.

The original intention was to calculate Symptom Appraisal time from the onset of symptoms until the point when subjects recognized the seriousness of their symptoms. However, 13 of the subjects sought medical attention for their symptoms while still believing that they were probably experiencing some benign condition. That is, these patients only realized that their symptoms were serious after their physician told them so. Symptom Appraisal time was thus calculated from symptom onset until either the recognition of seriousness or the visit to a doctor, whichever came first. Symptom Appraisal time ranged from less than a week to around 2 years, with a mean of 17.3 weeks (± 24.0) and a median of 7.0 weeks. On average, then, the time spent in Symptom Appraisal accounted for approximately 69.8% of the total time prior to medical consultation. Sixteen of the 63 subjects (25.4%) took 6 months or more to arrive at the conclusion that their symptoms might be serious, while 8 (12.7%) took 1 year or more.

Because thirteen of the subjects sought medical attention for their symptoms while still believing that they represented some benign condition, calculations of Action Appraisal time was based on the remaining 50 subjects. Action Appraisal time ranged from less than a week to around 5 years, with a mean of 9.7 (± 35.4) weeks and a median of 1.0 week. The correlation between the two time segments was marginally significant (Spearman's $\rho = 0.263$, $p = 0.065$), indicating that those subjects who spent more time in Symptom Appraisal also tended to spend more time in Action Appraisal.

Time-to-event analyses were conducted to determine the association between the two psychological measures (TCI-HA and STAI-T) and the length of Symptom Appraisal time, with the event of interest being the point at which the subjects recognized the seriousness of their symptoms. In addition, the relevant demographic variables were included in these analyses, given previous findings and interest in these patient characteristics. The 13 subjects who sought medical attention for their symptoms while still believing that they probably represented some benign condition were censored. As in the pilot work, scores on the two psychological measures were highly correlated (Spearman's $\rho = 0.58$; $p < 0.0001$; two-tailed), so separate analyses were completed for each of them. The first time-to-event analyses predicting Symptom Appraisal time included the following variables: TCI-HA, age at diagnosis, sex, and education. Unfortunately, ethnicity could not be included due to the very low number of minority subjects. The global null hypothesis was rejected (chi-square = 15.50; $p = 0.0084$; $df = 5$), indicating that Symptom Appraisal time was significantly related to some combination of these four variables. As seen in Table 1, those subjects who scored in the lowest tertile on the TCI-HA took significantly longer to realize that their symptoms were serious as compared with subjects in the middle and high tertiles. In addition, longer Symptom Appraisal times were also significantly related to fewer years of education (high school or less). There was also a nonsignificant tendency ($p = 0.059$) for younger subjects to take longer in Symptom Appraisal. The second time-to-event analysis simply substituted STAI-T for TCI-HA, and the global null hypothesis was very nearly rejected (chi-square = 10.80; $p = 0.0556$; $df = 5$). As seen in Table 2, younger subjects again took longer in Symptom Appraisal time, but no other variables were predictive. Two remaining time-to-

event analyses were performed, using the same variables as those above but predicting Action Appraisal time instead of Symptom Appraisal time. In neither case did the analysis result in rejection of the global null hypothesis.

Single variable Kaplan–Meier analyses were then conducted in order to provide estimates of median Symptom Appraisal times for subgroups of patients according to their psychological scores, age, sex, and education. As seen in Table 3, low scorers on the TCI-HA took much longer (30 weeks) in Symptom Appraisal than the middle (9 weeks) and high (12 weeks) scorers. On the other hand, there was very little difference by STAI-T score or sex. The trend by age is also shown, with the oldest group taking less time (7 weeks) in Symptom Appraisal than the others. Lastly, patients with fewer years of education took longer than those with more years of education (15 vs 8 weeks).

The final analyses explored relationships between the two psychological measures of Trait Anxiety and subjects' answers to questions about previous health-related judgments and behaviors. As seen in Table 4, lower scores on the TCI-HA were related to more favorable judgments of prior overall health. A test of the relationship between these two variables using the Kruskal-Wallis statistic was significant ($p = 0.039$). Lower TCI-HA scores also were related to less frequent doctor visits prior to cancer diagnosis, although this relationship did not reach statistical significance ($p = 0.07$). Low scores were also related to lower likelihood of cancer screening of any kind prior to their cancer diagnosis, and this relationship did reach statistical significance ($p = 0.040$). There was no apparent relationship between TCI-HA score and history of colorectal cancer screening, specifically. Similar analyses were done using the same health behavior questions and STAI-T tertile. In this case, lower scores were associated with more favorable judgments of overall prior health ($p = 0.025$) and with fewer doctor visits ($p = 0.041$), but were not associated with cancer screening or colorectal cancer screening.

DISCUSSION

The purpose of this work was to investigate dispositional characteristics associated with delays in seeking help for symptoms of rectal cancer. In several respects, findings from this study were in accordance with previous reports of delayed help seeking for symptoms of cancer. For example, delay in seeking help was a problem for a number of these patients, with over 17% waiting one year or more, suggesting that there has been little progress in reducing the problem of delay when compared with earlier findings (Hansen *et al.*, 1997; Holliday and Hardcastle, 1979; Irvin and Greaney, 1977; MacArthur and Smith, 1984; Robinson *et al.*, 1986; Rubin *et al.*, 1980). However, inspection of these data also revealed that delay times were skewed, as has been found in most studies of delay (Andersen *et al.*, 1995; Hackett *et al.*, 1973; Safer *et al.*, 1979; Worden and Weisman, 1975), showing that most people do act fairly quickly in response to symptoms. Also, this study provided more evidence that the minimization of symptoms during the Symptom Appraisal process is the major psychological culprit in delayed help seeking. Most patients tended to initially attribute their symptoms to some benign process such as hemorrhoids, and the method of delay time segmentation revealed that the Symptom Appraisal process accounted for the majority of total delay time, on average (Andersen *et al.*, 1995; Cacioppo *et al.*, 1986; Safer *et al.*, 1979). Together, these findings suggest a normative tendency to downplay the seriousness of ambiguous symptoms (Andersen *et al.*, 1995), which then resulted in delayed help seeking.

But the central aim of this work was to explore the role of broad and stable individual differences related to delay in seeking help for symptoms of rectal cancer. In that regard, these data provide evidence that some individuals tended to minimize their symptoms for a

longer period of time than others and that this tendency was related to a more global personality disposition, characteristic of people who are generally less responsive to threatening stimuli in their environments (Cloninger, 1987). The TCI-HA measure tends to focus on the cognitive aspect of anxiety (i.e. worry), with questions that tap the person's typical response to threatening or ambiguous situations (e.g. 'I often feel tense and worried in unfamiliar situations, even when others feel there is no danger at all.'). On the other hand, the STAI-T, which is designed to capture both the cognitive and somatic aspects of anxiety, was not related to Symptom Appraisal time. Recent research has shown that the cognitive and somatic aspects of anxiety are dissociable (Heller *et al.*, 1997; Nitschke *et al.*, 1999), and the present study suggests that the cognitive aspect (i.e. a decreased tendency toward worry) may be more strongly associated with longer Symptom Appraisal times.

There was some evidence, albeit not particularly strong, that younger age and less education were also related to longer Symptom Appraisal times. This evidence regarding less education is consistent with the prevailing literature (Andersen *et al.*, 1995; Antonovsky and Hartman, 1974; Facione, 1993; Facione *et al.*, 2002; Ramirez *et al.*, 1999; Samet *et al.*, 1988). As mentioned in the introduction, the evidence for association between age and delay has been inconsistent in the literature, with some studies showing that older patients delayed longer (Arndt *et al.*, 2002; Coates *et al.*, 1992; Ramirez *et al.*, 1999), others showing the reverse (Andersen *et al.*, 1995). Inconsistencies may have to do with the site of the cancer, the segment of delay being measured, and prevailing beliefs about the nature of certain diseases and their symptoms. Younger delayers may have lower perceived risk of colorectal cancers.

Also, lower levels of Trait Anxiety were variously related to other indicators of a history of lax health behaviors. These findings, though preliminary, might provide an intriguing link to previous clinical observations and research. That is, some have suggested that proximal causes of delay are related to more generalized and long-standing habits of health behavior. For example, it has long been observed clinically that people seem to respond to their cancer symptoms in much the same way that they had responded to previous medical or help-seeking situations (Coates *et al.*, 1992; Goldsen, 1963; Green and Roberts, 1974; Hackett *et al.*, 1973; King and Leach, 1950). In a large study of delay in patients with cancer symptoms, Hackett and colleagues asked subjects two related questions: (1) 'Do you tend to put off seeing your doctor?' and (2) 'Did you put it off this time?' The association between affirmative answers to these questions was highly significant (Hackett *et al.*, 1973). In another study, women who had utilized health services (e.g. routine dental exams, breast health exams) to a lesser extent over the previous 6 years waited longer to seek help for symptoms of breast cancer (Coates *et al.*, 1992). So, the fact that someone delays seeking help for their cancer symptoms may simply be one manifestation of some larger pattern of health-related behavior, which was probably established long before the onset of their present symptoms. The present study provides some evidence that the constellation of lax health behaviors that is seen in some people might also include a dispositional tendency to not worry, even in the face of health-threatening situations.

There are two principal limitations to the present study. First, it is retrospective, which presents challenges to the collection of maximally reliable data and the drawing of valid causal inferences. The reliability of these data depends on patients' recall of events that may have occurred up to several years in the past. But since patient delay is, by definition, a time period during which important physical symptoms are occurring without the benefit of appropriate clinical attention, it is a phenomenon for which retrospective investigation is the only reasonable alternative. The long-term goal of this research is to develop more effective methods of reaching those individuals who, left to their own devices, are most likely to delay seeking medical consultation when symptoms arise. Hence, the purpose of this study

was to begin to develop psychological characterizations of individuals who *did* delay seeking treatment, having been left to their own devices. An indirect causal argument could be made by noting that TCI-HA scores have been shown to be extremely stable over time (Cloninger *et al.*, 1994). In addition, recent studies have shown that TCI-HA scores are highly heritable (Heath *et al.*, 1994) and are also related to the size of specific brain structures (Pujol *et al.*, 2002) as well as measures of brain functioning (Hansenne, 1999; Hansenne and Ansseau, 1999) that seem to be involved in responsiveness to threat. These findings would suggest that whatever levels of Harm Avoidance were measured at the time of the present study were probably close to what might have been measured prior to symptom onset.

The second limitation to this study is that all data are provided by patients' self-reports. The biggest threat to validity posed by the self-report format is that those patients who took the longest to seek help may have tended to underreport their delay times out of shame or embarrassment (Coates *et al.*, 1992). But the present findings regarding lengths of delay times are consistent with many other studies (Holliday and Hardcastle, 1979; Irvin and Greaney, 1977; MacArthur and Smith, 1984; Rubin *et al.*, 1980), and the fact that a fair number of these patients reported very long delay times suggests that they were probably not intentionally minimizing the facts.

Some variables that have been found to be associated with delay might be subject to direct intervention and change, such as economic or logistic barriers. The evidence presented here suggests that one aspect of personality disposition is related to slower response to symptoms as well as a decreased likelihood of engaging in other preventive behaviors. While the psychological characteristics investigated in this report are not easily alterable, they could provide direction for future public health initiatives. A clearer understanding of the psychological characteristics of this at-risk audience could inform us as to how we can tailor and present educational materials most effectively.

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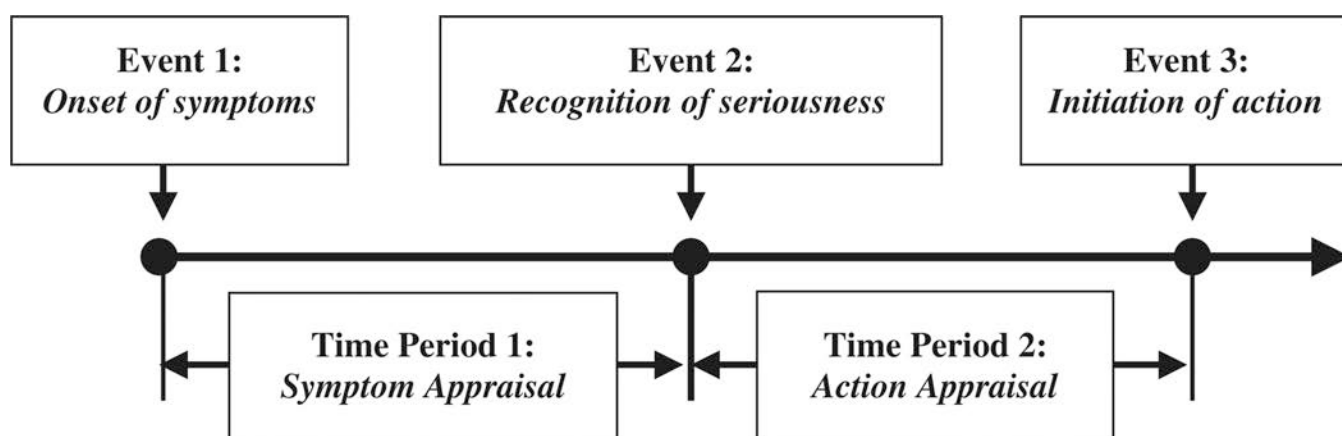


Figure 1.
Model of patient delay.

Table 1

Time-to-event analyses for TCI-HA tertile, age, sex, and education predicting symptom appraisal time

Variable	Hazard ratio	95% Confidence limits	<i>p</i>
TCI-HA			
Low	0.23	0.091–0.60	0.0024
Middle	0.63	0.31–1.30	0.21
High	1.00		
Age at diagnosis (Per year increase)	1.02	0.999–1.05	0.059
Sex			
Male	1.42	0.72–2.78	0.31
Female	1.00		
Education			
H.S. or less	0.49	0.26–0.94	0.030
> H.S.	1.00		

Table 2

Time-to-event analyses for STAI-T tertile, age, sex, and education predicting symptom appraisal time

Variable	Hazard ratio	95% Confidence limits	<i>p</i>
STAI-T			
Low	0.59	0.29–1.20	0.14
Middle	1.33	0.62–2.85	0.46
High	1.00		
Age at diagnosis (Per year increase)	1.03	1.004–1.06	0.025
Sex			
Male	1.08	0.56–2.09	0.82
Female	1.00		
Education			
H.S. or less	0.59	0.33–1.07	0.084
> H.S.	1.00		

Table 3

Single-variable Kaplan–Meier estimates of median symptom appraisal times

Variable	Median time (weeks)	95% Confidence limits	<i>n</i>
TCI-HA			
Low	30.0	(12.0, 78.0)	19
Middle	9.0	(4.0, 17.0)	24
High	12.0	(4.0, 26.0)	19
STAI-T			
Low	15.0	(4.0, 30.0)	20
Middle	9.0	(2.0, 26.0)	18
High	12.0	(4.0, 26.0)	23
Age at diagnosis			
33–51	13.0	(4.0, 65.0)	15
52–61	15.0	(3.0, 26.0)	16
62–70	14.0	(4.0, 26.0)	16
71–85	7.0	(2.0, 9.0)	16
Sex			
Male	12.0	(4.0, 26.0)	38
Female	13.0	(5.0, 20.0)	25
Education			
H.S. or less	15.0	(9.0, 26.0)	36
> H.S.	8.0	(4.0, 15.0)	27

Table 4

Relationships between psychological measures and responses to health behavior questions

Health behavior question	TCI-HA	STAI-T
'How would you describe your overall health before you were diagnosed with cancer?'	8.35 (<i>p</i> = 0.039)	9.33 (<i>p</i> = 0.025)
'How often did you go to your doctor before these problems began?'	6.99 (<i>p</i> = 0.07)	8.25 (<i>p</i> = 0.041)
'Have you ever had screening for any kind of cancer?'	4.20 (<i>p</i> = 0.040)	1.99 (<i>p</i> = 0.16)
'Have you ever been screened for colon or rectal cancer?'	0.01 (<i>p</i> = 0.91)	0.10 (<i>p</i> = 0.75)

Note: Numbers indicate Kruskal–Wallis test of association.